ly 10% of patients with bailout stents. Given the above assumptions, 30 patients per arm (with the analysis of 22 evaluable patients per arm) will provide 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) would provide more than 96% power.

Binary variables were compared using Fisher's Exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon Rank-Sum test, except for the primary endpoint which was evaluated with a one sided *t*-test. Final 6-month results are presented in the manuscript, while the Appendix contains results that were available at the time that the 180-day report was prepared.

Results

Patient characteristics

Between December 2003 and April 2004, 28 patients were randomly assigned to receive the everolimus-eluting stent, and 32 were assigned to receive the bare stent. As defined in the protocol, all results (except acute success) are presented for the per-treatment population (27 patients in the everolimus group, and 29 patients in the bare stent group, Figure 1). In the everolimus group there was one bailout procedure, and in the bare stent group there were two bailout procedures and one major protocol deviation (the patient was on the heart transplant waiting list). With the exception of a significantly higher number of patients with hypertension requiring treatment in the everolimus group, the two groups were similar with respect to clinical variables examined (Table 1).

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

Age(yrs)	64 ± 10	61 ± 9	63 ± 9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring medication (%)	70	41	55
Hyperlipidemia requiring medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left anterior descending	48	45	46
Left circumflex	22	21	21
RCA	30	34	32
AHA / ACC Lesion Class (%)**			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference Vessel Diameter (mm ± SD)	2.61 ± 0.40	2.71 ± 0.28	2.66 ± 0.34
Lesion length (mm ± SD)	10.1 ± 2.6	10.9 ± 3.3	10.5 ± 3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)

** AHA / ACC = American Heart Association / American College of Cardiology

FIGURE 1

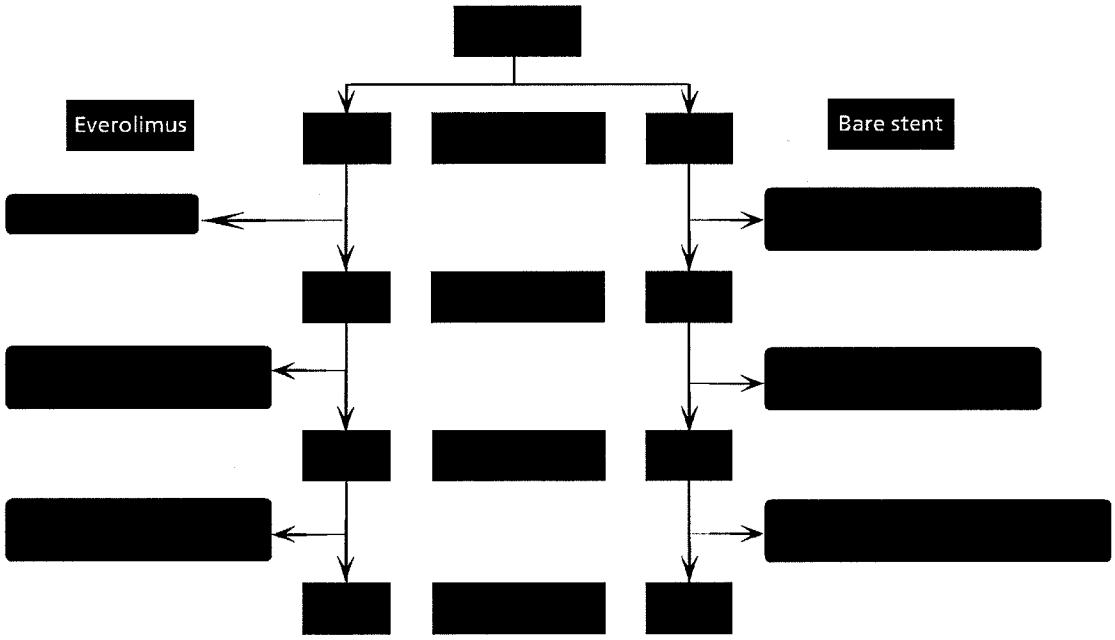

Fig. 1: Flowchart of patients

Procedural characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Glycoprotein IIb/IIIa inhibitors, used at the investigators' discretion, were administered to 7.4% of the patients in the everolimus group and 3.4% of those in the bare stent group. The two groups did not differ significantly with respect to the rate of device success (96.4% in the everolimus group and 93.8% in the bare stent group) or clinical success (96.4% in the everolimus group and 100% in the bare stent group).

Quantitative coronary angiography analysis

Angiographic data at 6 months were available for 50 of the 56 analysable patients (89.3%). The mean reference diameter of the target vessel, the mean length of the lesion at baseline, the reference vessel diameter and mean MLD of the stented segment were similar in the two groups (Tables 1 and 2). At six months, with matched pairs analysis, the mean MLD of the stented segment was significantly greater in the everolimus group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were 0.10 mm, 16%, and 0%, respectively, in the everolimus group, as compared with 0.87 mm, 39%, and 25.9%, respectively, in the bare stent group ($p<0.001$ for late loss and diameter stenosis, $p=0.01$ for restenosis). Figure 2 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 and Figure 3 show the results of sub-segmental quantitative angiographic analyses for matched pairs. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus group than in the bare stent group ($p <0.01$ for proximal and $p=0.04$ for distal). The late luminal loss in the stented segment was significantly less in the everolimus group than in the bare stent group ($p \leq 0.001$).

Intravascular ultrasound evaluation

At six months follow-up, intravascular ultrasound evaluation showed no significant differences between the two groups with respect to the volume of the stent or the vessel volume (Table 3). Significantly

FIGURE 2

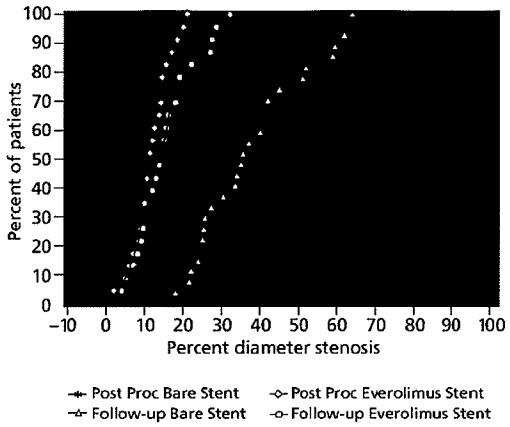

Fig. 2: Cumulative frequency of stenosis (in-stent) immediately after stenting and at six months

FIGURE 3

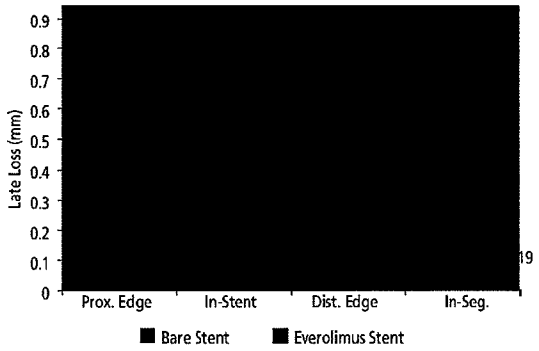

Fig. 3: Comparison of in-segment / in-stent late loss

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Matched Pairs).

Reference Vessel Diameter (mm)												
After procedure	2.80 ± 0.33	3.04 ± 0.38	0.06*	2.71 ± 0.28	2.89 ± 0.35	0.11*	2.64 ± 0.30	2.80 ± 0.39	0.21*	2.65 ± 0.30	2.84 ± 0.41	0.10*
At 6 months	2.78 ± 0.32	2.67 ± 0.40	0.22*	2.70 ± 0.31	2.58 ± 0.37	0.25*	2.61 ± 0.37	2.46 ± 0.36	0.19*	2.61 ± 0.36	2.59 ± 0.36	0.89*
Minimal Luminal Diameter (mm)												
After procedure	2.56 ± 0.44	2.61 ± 0.45	0.79*	2.38 ± 0.25	2.45 ± 0.31	0.50*	2.23 ± 0.41	2.26 ± 0.45	0.77*	2.11 ± 0.35	2.14 ± 0.40	1.00*
At 6 months	2.45 ± 0.46	2.19 ± 0.49	0.04*	2.28 ± 0.33	1.58 ± 0.41	< 0.001*	2.18 ± 0.38	2.00 ± 0.45	0.21*	2.04 ± 0.40	1.54 ± 0.41	< 0.001*
Late Loss (mm)	0.11 ± 0.15	0.42 ± 0.39	<0.01*	0.10 ± 0.21	0.87 ± 0.37	< 0.001***	0.05 ± 0.20	0.26 ± 0.40	0.04*	0.07 ± 0.19	0.61 ± 0.37	< 0.001*
Diameter Stenosis (%DS)												
After procedure	9 ± 11	14 ± 9	0.07*	12 ± 5	15 ± 6	0.05*	16 ± 10	20 ± 10	0.16*	20 ± 8	24 ± 9	0.05*
At 6 months	12 ± 12	17 ± 17	0.26*	16 ± 8	39 ± 14	< 0.001*	16 ± 10	19 ± 14	0.82*	22 ± 11	41 ± 14	< 0.001*
Binary Restenosis Rates	4.3%	3.7%	1.00**	0.0%	25.9%	0.01**	0.0%	7.4%	0.49**	4.3%	33.3%	0.01**

* two-sided Wilcoxon rank sum test ** two-sided Fisher's Exact test *** One-sided t-test † Fisher's Exact test

Table 3. IVUS measurements at 6 month follow-up.

Vessel volume (mm^3)	291 ± 82	296 ± 73	0.64
Stent volume (mm^3)	134 ± 28	139 ± 33	0.69
In-stent neo-intimal volume (mm^3)	10 ± 13	38 ± 19	<0.001
Luminal volume (mm^3)	124 ± 32	100 ± 31	0.04
In-stent volume obstruction (%)**	8.0 ± 10.4	28.1 ± 14.0	<0.001

* This final table contains an additional 13 patients not included in the 180-day report prepared for the sponsor. In 8 patients (4 in each group), an imputed stent length of 18mm was used due to non-continuous pullback. In a further 5 patients (all bare stent group) results were unavailable at the time of the 180-day report. (see Appendix)

** In-stent volume obstruction = 100*
(In-stent neo-intimal volume / Stent volume)

less neointimal hyperplasia was observed in the everolimus-stent group compared to the bare-stent group (10 ± 13 vs. 38 ± 19 mm^3, p<0.001) and similarly, significantly less volume obstruction, (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). Figure 4 is a cumulative curve of percentage volume obstruction. No in-stent volume obstruction was detected in almost half of the patients in the everolimus-stent group, whereas in the bare stent group, some degree of obstruction by neointima was present in all patients (Figure 4). No evidence of an "edge effect," aneurysm formation, in-stent thrombosis, persistent dissection or late incomplete apposition were observed.

FIGURE 4

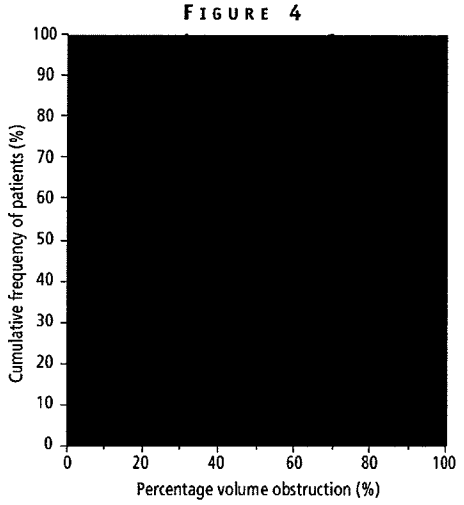

Fig. 4: Percentage in-stent volume obstruction versus cumulative frequency of patients. Values are expressed as mean ± standard deviation for each group.

Major adverse cardiac events

Major adverse cardiac events are listed in Table 4. There was one Q-wave myocardial infarction in the everolimus group in a patient who underwent additional revascularization for angina in a non-target vessel 18 days after the study procedure and suffered thrombosis of this non-study stent 12 days later. The everolimus stent was patent with no evidence of thrombus at the time of the thrombotic occlusion of the non study stent. One patient in the everolimus arm underwent a clinically driven target lesion revascularization at 3 weeks for symptomatic persistent dissection at the proximal edge left untreated at the time of the procedure. There were no clinically driven target revascularizations in the everolimus group for restenosis. There were six clinically driven target lesion revascularizations in the bare stent group, five were treated percutaneously for restenosis and the sixth by bypass surgery. No adverse effects were attributable to everolimus or the polymer coating of the stents.

Table 4. Hierarchical major adverse cardiac events at 180 days in per-treatment population*.

Cardiac death	0	0	0	0
Myocardial infarction				
Q-wave	1‡	3.8	0	0
Non-Q-wave	0	0	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	1 §	3.8	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	2	7.7	6	21.4
Major adverse cardiac events	2	7.7	6	21.4

* One patient in each group withdrew consent after treatment
** No statistical significance was detected between groups for all endpoints tested.
‡ Q-wave MI due to thrombosis of a non-study stent in a non-target vessel.
§ Clinically driven TLR for persistent dissection proximal to the stent 3 weeks after the index procedure.

Discussion

The main finding of this randomized first-in-man study is that an everolimus-eluting stent coated with a durable polymer was associated with an in-stent angiographic late loss of 0.10 mm, significantly less than the corresponding bare cobalt chromium metal stent of 0.87 mm, which satisfied the primary endpoint of this trial and confirmed the efficacy of this system. Correspondingly, in-segment late loss was also significantly less in the everolimus-stent group.

Currently, two different drug-eluting systems (sirolimus and paclitaxel) are available. Although no published scientific comparative data is to date available, it appears that, from historical randomized trials, a difference of approximately 0.2 mm in-stent late loss exists between sirolimus and paclitaxel. Even if the impact of restenosis and MACE is currently unknown, some slight difference in restenosis rates and MACE can be expected. New devices should at least equal the incumbents in performance. This performance may be judged on late

loss, restenosis rate and / or the need for reintervention. With an in-stent late loss ranging from zero to 0.2 mm, it has been difficult to find a compound with the same efficacy, without resorting to the -limus family (Figure 5). With the sirolimus molecule being rather large and complex, it is therefore not surprising that major pharmaceutical companies have thoroughly explored its numerous analogues in order to develop a suitable competitor to sirolimus. The drug used in this study, everolimus differs from sirolimus by a substitution of a hydrogen radical/side-branch with a methyl sidechain.

FIGURE 5

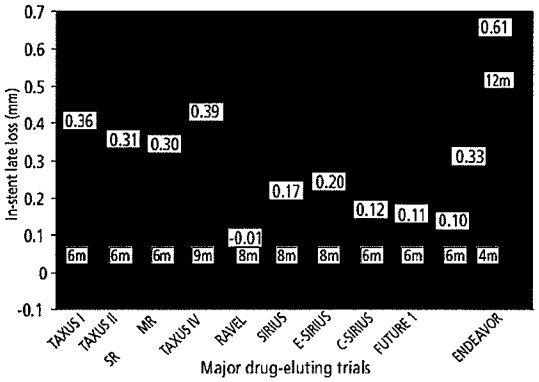

Fig. 5: Comparison of in-stent late loss from drug-eluting trials.

The reason for developing new compounds is to improve on the side effects of the existing compounds such as delayed healing with re-endothelialization and fibrin[11], early[12] and late stent thrombosis[13]. The success of the device lies in its three components - the drug, the polymer properties and the stent. The use of a sirolimus analogue is not in itself a guarantee of success since some of them have intrinsically, a potency in inhibition of up to 100 times less (e.g. tacrolimus), and some other analogues with equal *in vitro* inhibitory effects nevertheless fail to equally inhibit neointimal growth *in vivo*, because their duration of elution was suspected to be too short. However it has already been demonstrated that everolimus in clinical trials using a bioerodable polymer with a slower elution profile than sirolimus is effective in reducing late loss to below 0.2 mm[4]. Therefore the remaining challenge was to establish whether everolimus eluted from a durable polymer was also efficient and is addressed in this report.

Although the 6-month results are promising, one year angiographic and IVUS follow-up results are awaited to confirm the long-term results of this device in light of recent findings regarding an increasing late loss seen with other devices over time.

At the time of the publication of RAVEL, it was argued that the restenosis rate of the bare stent was excessively high at 26%. Similarly, in the present trial the restenosis rate in the bare stent arm was 25.9%. Nevertheless, it must be emphasized that in both cases these restenosis rates correspond to the value predicted and derived from multivariate analyses including as determinant parameters vessel size, MLD post, incidence of LAD disease and diabetics. Of interest, the late loss of the bare stent groups in RAVEL and this study were similar, corresponding to their restenosis rates. This is at variance with the VISION registry, and publications on stent strut thickness, but may be explained by the mismatch in stent size and reference diameter.

This study was powered for late loss and not for clinical events, and it was not surprising that the 3 fold reduction in events failed to be statistically significant. At the time of trial design, safety studies with overlapping eluting-stents in animal models had not been completed, requiring the use of bare stents for bailout. As a result of this confounder, these patients were *a priori* excluded from the per-treatment analysis. This study was however designed as a first in man trial with everolimus on an untested new durable polymer in combination with a cobalt chromium stent.

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Appendix

Sponsor: Guidant Corporation, Santa Clara, California, USA.

Principal Investigator: Patrick W. Serruys (The Netherlands).

Executive Committee: P.W. Serruys (Principal Investigator and Chairman, Rotterdam, The Netherlands); Gary Johnson (Vice President of Regulatory Affairs/Clinical Research, Guidant Corporation); Stan Fink (Director of Clinical Research USA, Guidant Corporation).

Data Safety Monitoring Board (DSMB) - J.G.P. Tijssen, Amsterdam, The Netherlands; F.W.A. Verheugt, Nijmegen, The Netherlands; W. Wijns, Aalst, Belgium.

Clinical Events Committee (CEC) - J. Vos, Amphia Ziekenhuis, Breda, The Netherlands; B.J.W.M. Rensing, Sint Antonius Ziekenhuis, Nieuwegein, the Netherlands; C. Hanet, Clinique Universitaire de Saint-Luc, Brussels, Belgium.

Data management - Angiographic and IVUS core laboratories: Cardialysis BV, Rotterdam, The Netherlands; Data Coordination Centre and Site Monitoring: Guidant Europe, Diegem, Belgium.

The following investigators and institutions participated in the SPIRIT First trial:

Clinical sites: J.J. Piek, Academisch Medisch Centrum, Amsterdam, The Netherlands (18 patients); F.J. Neumann, Herzzentrum, Bad Krozingen, Germany (14 patients); P.W. Serruys, Thoraxcentre, Erasmus Medical Centre, Rotterdam, The Netherlands (5 patients); M. Wiemer, HZ Herzzentrum, Bad Oeynhausen, Germany (5 patients); A. Zeiher, Uni. Klinikum Frankfurt, Frankfurt, Germany (4 patients); E. Grube, Heart Center Siegburg, Siegburg, Germany (4 patients); J. Haase, Red Cross Hospital, Frankfurt, Germany (4 patients); L. Thuesen, Skejby Sygehus, Aarhus, Denmark (4 patients); C. Hamm, Kerckhoff Klinik, Bad Nauheim, Germany (2 patients).

Table A2. Appendix: results of intra vascular ultra sound analysis as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

Vessel volume (mm^3)	299 ± 87	284 ± 77	0.76
Stent volume (mm^3)	138 ± 30	139 ± 39	1.00
In-stent neo-intimal volume (mm^3)	11.2 ± 14.0	41.4 ± 20.1	<0.001
Luminal volume (mm^3)	126 ± 35	98 ± 34	0.06
In-stent volume obstruction (%)	8.6 ± 10.7	29.0 ± 13.9	<0.001

Table A1. Appendix: results of sub-segmental quantitative coronary angiographic analysis (Unmatched Pairs) as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value
After procedure	2.49 ± 0.44	2.57 ± 0.39	0.44*	2.34 ± 0.26	2.42 ± 0.31	0.41*	2.18 ± 0.44	2.25 ± 0.42	0.67*	2.07 ± 0.37	2.14 ± 0.37	0.74*
At 6 months	2.45 ± 0.46	2.19 ± 0.50	0.05*	2.28 ± 0.33	1.58 ± 0.42	<0.001*	2.18 ± 0.38	1.99 ± 0.46	0.19*	2.04 ± 0.40	1.53 ± 0.41	<0.001*
Late loss (mm)	0.10 ± 0.17	0.38 ± 0.38	0.01*	0.10 ± 0.23	0.84 ± 0.36	<0.001***	0.07 ± 0.20	0.26 ± 0.41	0.14*	0.09 ± 0.20	0.60 ± 0.36	<0.001*
After procedure	10 ± 10	15 ± 9	0.13*	12 ± 4	15 ± 6	0.02*	17 ± 10	19 ± 9	0.39*	21 ± 8	24 ± 8	0.14*
At 6 months	12 ± 12	18 ± 17	0.21*	16 ± 8	39 ± 14	<0.001*	16 ± 10	20 ± 14	0.67*	22 ± 11	41 ± 14	<0.001*
Binary restenosis rates	4.3%	3.8%	1.00**	0.0%	26.9%	0.01**	0.0%	7.7%	0.49**	4.3%	34.6%	0.01**

* Two-sided Wilcoxon rank sum test ** Two-sided Fisher's Exact test *** One-sided t-test

European Heart Journal (2001) 22, 1938–1947
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The TRAPIST Study

A multicentre randomized placebo controlled clinical trial of trapidil for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound

P. W. Serruys[1], D. P. Foley[1], M. Pieper[2], J. A. Kleijne[3] and P. J. de Feyter[1] on behalf of the TRAPIST investigators

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Background Studies have reported benefit of oral therapy with the phosphodiesterase inhibitor, trapidil, in reducing restenosis after coronary angioplasty. Coronary stenting is associated with improved late outcome compared with balloon angioplasty, but significant neointimal hyperplasia still occurs in a considerable proportion of patients. The aim of this study was to investigate the safety and efficacy of trapidil 200 mg in preventing in-stent restenosis.

Methods Patients with a single native coronary lesion requiring revascularization were randomized to placebo or trapidil at least 1 h before, and continuing for 6 months after, successful implantation of a coronary Wallstent. The primary end-point was in-stent neointimal volume measured by three-dimensional reconstruction of intravascular ultrasound images recorded at the 6 month follow-up catheterization.

Results Of 312 patients randomized at 21 centres in nine countries, 303 (148 trapidil, 155 placebo) underwent successful Wallstent implantation, and 139 patients (90%) in the placebo group and 130 (88%) in the trapidil group had repeat catheterization at 26 ± 2 weeks. There was no significant difference between trapidil and placebo-treated patients regarding in-stent neointimal volume (108·6 ± 95·6 mm^3 vs 93·3 ± 79·1 mm^3; P=0·16) or % obstruction volume (38 ± 18% vs 36 ± 21%; P=0·32), in angiographic minimal luminal diameter at follow-up (1·63 ± 0·61 mm vs 1·74 ± 0·69 mm; P=0·17), restenosis rate (31% vs 24%; P=0·24), cumulative incidence of major adverse cardiac events at 7 months (22% vs 20%; P=0·71) or anginal complaints (30% vs 24%; P=0·29).

Conclusion Oral trapidil 600 mg daily for 6 months did not reduce in-stent hyperplasia or improve clinical outcome after successful Wallstent implantation and is not indicated for this purpose.

(Eur Heart J 2001; 22: 1938–1947, doi:10.1053/euhj.2001.2627)

Key Words: Restenosis, stent, trapidil, intravascular ultrasound, quantitative coronary angiography, randomized trial.

See page 1847 for the Editorial comment on this article

Introduction

Stenting reduces restenosis and repeat revascularization compared with balloon angioplasty in selected patients with single vessel coronary artery disease[1,2]. With increased rates of stent use and application to complex and multivessel disease, however, in-stent restenosis may be observed in up to one third of patients[3] and due to its indolence, prevention using effective antiproliferative measures remains a high priority.

The phosphodiesterase inhibitor, trapidil, a potent inhibitor of platelet derived growth factor and thromboxane A2 synthetase, inhibits cellular proliferation induced by platelet derived growth factor in-vitro and in-vivo[4–6] and was reported to reduce restenosis after coronary balloon angioplasty[7,8]. However, since post-angioplasty restenosis involves both rheologic and proliferative processes[9], we sought to evaluate the anti-proliferative potential of trapidil post-stenting, using the

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novel, recently described methodological approach of 3-D intravascular ultrasound measured in-stent neointimal volume as the primary end-point[10].

Methods

Primary end-point

Based on an expected in-stent neointimal volume of 125 mm^3 for Wallstents of 30 mm length[10–14], it was calculated that 240 evaluable patients would be necessary to detect a 30% reduction by trapidil, with 90% power (1-β), at two sided α of 0·05.

Study population

Patients with stable or unstable angina and/or documented ischaemia, scheduled to undergo single Wallstent implantation in a de novo coronary lesion ≤40 mm long in a vessel of 3–6 mm could be included. Exclusion criteria included: life expectancy <1 year, myocardial infarction within 7 days, left bundle branch block, side branch >2·0 mm, thrombus and left main lesion; those specific to trapidil therapy were: active peptic disease, bleeding disorder, stroke within 6 months and treatment with oral anticoagulants, ketanserin, ticlopidine, pentoxyphilline, calcium antagonists and molsidomine. The protocol was approved by the ethical board of participating hospitals and all patients gave written informed consent prior to inclusion.

Medication and stent implantation

A loading dose of ticlopidine (500–1000 mg) was given 12–48 h before stenting, and continued at 500 mg daily for 1 month. A minimum of 1 h before, one tablet of trial medication was administered (to allow Cmax serum level at the time of barotrauma[15]). Aspirin 75–500 mg was continued indefinitely. After arterial access, heparin 10 000 units was given parenterally. The self-expanding coronary Magic Wallstent® (Boston Scientific Corporation, Paris, France), was implanted after pre-dilatation and post-dilated to diameter stenosis of <20%. Intravascular ultrasound guidance was up to the treating physician, final post-procedural intravascular ultrasound being mandatory. After successful procedures, trial medication was given 8 h for 6 months, but withheld on the morning of follow-up exercise testing.

Angiographic and intravascular ultrasound procedures

Angiography in multiple projections was performed pre- and post-stenting and at the 6 month follow-up, and analysed at the angiographic core lab (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiographic Analysis System (CAAS II) as described elsewhere[1,3,16]. Post-stenting and at the 6 month follow-up, stented vessel segments were examined with mechanical intravascular ultrasound (CardioVascular Imaging System (CVIS), Sunnyvale, CA, U.S.A.) using automated pullback at 0·5 mm . s^{-1}. A computer based contour detection program was used for automated 3-D reconstruction of the stented segment from up to 200 cross-sectional images. Lumen and stent boundaries are detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as $V=\sum_{i=1}^{n} A_i \cdot H$, where V=volume, A=total vessel, stent or lumen area (as desired) in a given cross sectional image, H=thickness of the coronary artery slice, and n=number of slices[10–13]. Neointimal volume was calculated as stent volume − luminal volume.

Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated in vitro and in vivo[12–14] and a prior multicentre randomized clinical trial has been performed using this methodology[10]. Where intravascular ultrasound at follow-up was not available, an imputation programme was used employing intravascular ultrasound post-procedure and quantitative coronary angiography at follow-up, to impute the intravascular ultrasound data at follow-up, as follows:

(1) Regression equations established the relationship between intravascular ultrasound and quantitative coronary angiography mean luminal and stent diameter at follow-up in all lesions with complete data.
(2) Stent length at follow-up was determined by intravascular ultrasound post-stent or quantitative coronary angiography at follow-up, also based on the r-square of regression equations applied in patients with complete data.
(3) Luminal volume=stent length * mean luminal area.
(4) Imputed stent volume=imputed stent length * imputed mean stent area.
(5) Imputed neointimal volume=imputed stent volume − imputed lumen volume.
(6) In cases of stent occlusion, it was assumed that the stent was completely filled with tissue, so neointimal volume='luminal volume'.

Imputed data were entered in the database blind before the treatment code was broken, using the following generated regression equations:

Total occlusions

[1] Imputed stent length follow-up=6·217+0·709 * Stent length post from intravascular ultrasound.
[2] Imputed mean stent area follow-up=2·353+0·916 * Mean stent area post from intravascular ultrasound.
[3] Imputed stent volume=Imputed stent length * imputed mean stent area; Imputed neointimal volume=Imputed stent volume.

Table 1 Summary of patient disposition

	Placebo	Trapidil
Randomized (safety population)	158	154
No stent implantation	3	6
Reason		
Guidewire did not cross	2	2
Lesion not suitable for stenting	1	3
Good result after balloon angioplasty	0	1
Stent implantation successful (intention-to-treat population)	155	148
No 6 month follow-up intravascular ultrasound available	33	23
Reason		
Intravascular ultrasound device could not cross	9	2
Patent vessel	4	0
Total occlusion	5	2
Technical problems intravascular ultrasound	3	5
Refused recatherization	7	11
Major adverse cardiac events	9	7
Other	5	3
Intravascular ultrasound not analysable	7	5
Analysable intravascular ultrasound at 6 months	115 (74%)	120 (81%)
Intravascular ultrasound imputation	22	11
Treatment compliance	116	104
Per protocol population	111 (72%)	102 (69%)

No total occlusion

[1] Imputed stent length follow-up=2·773+1·047 * Stent length follow-up from quantitative coronary angiography.
[2] Imputed mean stent area follow-up=2·353+0·916 * Mean stent area post from intravascular ultrasound.
[3] Imputed mean in-stent lumen diameter follow-up=0·624+0·880 * Mean lumen diameter follow-up from quantitative coronary angiography.
[4] Imputed lumen volume=2 * π * (0·5 * Mean in-stent lumen diameter)^2.
[5] Imputed stent volume=imputed stent length * imputed mean stent area.
[6] Imputed neointimal volume=imputed stent volume − imputed lumen volume.

Secondary end-points

Intravascular ultrasound measured minimum luminal diameter (mm) and minimal luminal cross-sectional area (mm^2) and quantitative coronary angiography measured minimum luminal diameter (mm) at follow-up, late loss, restenosis rate and loss index.

Clinical outcome

Major adverse cardiac events were defined as:

Cardiac death: All deaths were considered cardiac unless documented otherwise.

Myocardial infarction: Either: new abnormal Q waves (Minnesota code) not present at baseline, or elevation more than twice the upper limit of normal of CK and CK-MB.

Target lesion revascularization: Re-PTCA or CABG was required to be preceded by documentation of anginal complaints and/or objective evidence of reversible ischaemia.

Anginal status was documented at each visit and an exercise test was performed within 2 weeks prior to repeat angiography.

Treatment compliance was defined, using pill counting, by 90% intake of trial medication at 1 month and 80% at 6 months.

Analytical and statistical plan

The intention-to-treat population comprised patients undergoing successful stent implantation after at least one capsule of trial medication. The primary end-point was evaluated in patients undergoing follow-up catheterization. The per protocol population comprised patients with successful stenting and evaluable follow-up intravascular ultrasound, who were compliant with medication and follow-up.

Outcome measures were compared using chi-square or Fisher's exact test for categorical variables and two-tailed Student's t-test for continuous variables. Major adverse cardiac events are presented using the Kaplan–Meier method and compared using a logrank test.

Table 2 Baseline demographic characteristics of the intention-to-treat population

	Placebo n=155	Trapidil n=148
Male	109 (70%)	120 (81%)
Age (years)	60 ± 9·5	60 ± 9·7
Previous myocardial infarction	70 (45%)	68 (46%)
Q wave	40 (26%)	43 (29%)
Non-Q wave	30 (19%)	25 (17%)
Previous CABG	6 (4%)	10 (7%)
Previous PTCA	25 (16%)	26 (18%)
Diabetes mellitus	21 (14%)	20 (14%)
Insulin dependent	6 (4%)	5 (3%)
Non-insulin dependent	15 (10%)	15 (10%)
Hypertension	65 (42%)	62 (42%)
Hypercholesterolaemia	86 (55%)	79 (53%)
History of stroke	4 (3%)	2 (1%)
Family history of CAD	68 (44%)	55 (37%)
Peripheral vascular disease	9 (6%)	17 (11%)
Smoking history		
Never smoked	45 (29%)	42 (28%)
Previous smoker	67 (44%)	71 (48%)
Current smoker	41 (27%)	35 (24%)
Unstable angina	55 (35%)	54 (36%)
Braunwald classification		
IB	15 (10%)	13 (9%)
IIB	26 (17%)	27 (18%)
IC	6 (4%)	7 (5%)
IIC	8 (5%)	7 (5%)
Stable angina	90 (58%)	85 (57%)
Canadian Cardiovascular Society classification		
1	3 (2%)	3 (2%)
2	36 (23%)	31 (21%)
3	42 (27%)	41 (28%)
4	9 (6%)	10 (7%)
Silent ischaemia	10 (6%)	9 (6%)

CAD=coronary artery disease.

Results

Patient disposition (Table 1), demographics (Table 2), procedural intravascular ultrasound and quantitative coronary angiography (Table 3)

Patients exhibited a high frequency of risk factors and two thirds had complex lesions (type B2 or C). Target lesions were located less frequently in the left coronary artery, due to risk of imprisoning important diagonal or marginal branches. Wallstents were successfully implanted in 303 of the 312 randomized patients (Table 1). Additional stents were required in 17%. Mean implanted stent length was 30 ± 13 mm. Five patients experienced peri-procedural non-Q wave myocardial infarction and two underwent CABG before discharge.

Efficacy analysis (Table 4, Fig. 2)

Imputation was required in 33 patients. The primary end-point was evaluated in 89% and 88% of patients in the trapidil and placebo groups, respectively. There was no significant difference in in-stent neointimal volume or % obstruction.

Secondary end-points (Table 5, Fig. 1)

No significant difference was observed in the minimal lumen diameter (mm) or minimal luminal cross-sectional area (mm^2) by intravascular ultrasound, or in minimal lumen diameter (mm), late loss, loss index or restenosis rate by quantitative coronary angiography.

Major adverse cardiac events and anginal status at 7 months (Tables 6, 7; Fig. 3)

There was no significant difference in the cumulative incidence of major adverse cardiac events during follow-up (the majority being target lesion revascularization) or in recurrence of angina.

Compliance and side effects

Compliance, as defined above, was 76% in patients on trapidil and 83% on placebo at 1 month and 70% and 75% at 6 months. A total of 54% of patients in the placebo group and 67% in the trapidil group reported adverse experiences, gastrointestinal disturbances being observed in 24% of trapidil and 12% of placebo-treated patients.

Discussion

Previous studies reporting restenosis reduction by trapidil after balloon angioplasty[6,7] failed to convince the cardiology community to prescribe it for this purpose. These studies revealed various deficiencies including: small study size, large number of patients lost to follow-up or retrospectively excluded and suboptimal methodology (e.g. visual or calliper method of angiographic evaluation). Recognizing these shortcomings and that restenosis after balloon angioplasty is multifactorial, this trial set out to definitively investigate the putative antiproliferative effects of trapidil[4,5,8,17–19] after stent implantation where restenosis is a proliferative process and by using the most objective methodology currently available, namely 3-D intravascular ultrasound and serial quantitative coronary angiography.

Our findings, in contrast to the prior studies, indicate that trapidil in an adequate dose regimen fails to reduce restenosis, whether measured by intravascular ultrasound, quantitative coronary angiography or occurrence of major adverse cardiac events. A recent small trial comparing trapidil with aspirin post Palmaz–Schatz stenting in 118 patients also found no difference in clinical or angiographic results[20]. It appears likely that the benefit reported in the previously mentioned studies is serendipidous.

Table 3 Baseline qualitative (pre-stenting) and quantitative (pre- and post-stenting) angiographic data and intravascular ultrasound assessment (post-stenting)

	Placebo n=155 patients	Trapidil n=148 patients
Qualitative angiography (n=303)		
Vessel dilated		
LAD	58 (37%)	48 (32%)
LCX	21 (14%)	26 (18%)
RCA	76 (49%)	74 (50%)
Lesion type (ACC/AHA classification)		
A	8 (5%)	11 (7%)
B1	52 (33%)	41 (28%)
B2	80 (52%)	83 (56%)
C	15 (10%)	13 (9%)
Quantitative angiography (n=299)	n=152*	n=147**
Pre-stenting		
Reference diameter (mm)	3·05 ± 0·47	3·00 ± 0·45
Minimal lumen diameter (mm)	0·95 ± 0·40	0·96 ± 0·35
Diameter stenosis (%)	68 ± 13	68 ± 11
Post-stenting		
Reference diameter (mm)	3·27 ± 0·43	3·23 ± 0·37
Minimal lumen diameter (mm)	2·77 ± 0·37	2·75 ± 0·33
Diameter stenosis (%)	15 ± 6	15 ± 7
Intravascular ultrasound post stenting (n=274)	n=136	n=138
Reference area (mm^2)	9·28 ± 3·78	9·41 ± 4·37
Minimal lumen area (mm^2)	6·11 ± 1·81	6·24 ± 1·89
Mean lumen area (mm^2)	7·79 ± 2·17	7·87 ± 2·09
Minimal lumen diameter (mm)	2·76 ± 0·41	2·79 ± 0·40
Projected minimal lumen diameter (mm)**	2·58 ± 0·40	2·59 ± 0·38
Stent symmetry ratio	0·91 ± 0·03	0·91 ± 0·03
Stent length (mm)	29 ± 14	29 ± 13
Stent volume (mm^3)	226 ± 135	228 ± 129

*Film not analysable due to overlap and foreshortening.
**Film not available for Corelab analysis.

Why did trapidil fail to prevent restenosis in this trial?

The reason for the failure of trapidil might be related to fundamental biological processes, drug pharmacokinetics, adequacy of the experimental basis and/or the clinical setting of the trial.

(1) Fundamental cell biology

Although stent restenosis may be considered a 'pure' proliferative process, interaction of multiple factors contributes to the ultimate formation of the neointima including clotting factors, cytokines, enzymes, growth factors, hormones, inflammatory cells etc. and probably other as yet unidentified molecules. Accordingly, even if the goal of a specific pharmacological intervention (e.g. inhibition of the Raf-1/MAP-kinase cascade by trapidil[8,19]), is successful, this could be counterbalanced by feed-back loops or other undefined pathways and be insufficient to inhibit the proliferative process.

(2) Pharmacokinetics

In contrast with the STARC trial[7], with pre-treatment of 3 days, there was no pre-treatment in this trial for logistic reasons, however, recent pharmacokinetic studies indicate that maximum plasma levels are reached 1 h after a single 200 mg tablet[15], so this should not be an issue. What may well be an issue is whether a sustained plasma level sufficient to inhibit hyperplasia could be reached by a three times daily dosage, since auto-induction of trapidil metabolism after repeated oral doses has been demonstrated, with an elimination half-life at steady-state of 1·19 ± 0·26 h[15].

(3) Adequacy of experimental models

The adequacy of the pre-clinical investigations as a basis for the balloon angioplasty studies could be criticised for being carried out in species no longer recognized as reliable forerunners for clinical evaluation (rabbit, rat, hamster[4,5]), using endothelial denudation, which is not a surrogate for single or double arterial injury, as is now considered appropriate.

(4) Appropriateness of the clinical setting

The Wallstent has been previously reported in non-randomized trials to be associated with a greater neointimal hyperplasia than other stents despite excellent acute results[13,11,14]. Continued stent self-expansion

Table 4 Six month follow-up intravascular ultrasound results

	Intention-to-treat without imputation			Intention-to-treat with imputation			Per protocol		
	Placebo n=115	Trapidil n=123	*P*-value	Placebo n=137	Trapidil n=151	*P*-value	Placebo n=111	Trapidil n=102	*P*-value
Ref. area (mm^2)	8·95 ± 3·71	8·56 ± 3·19	0·60	8·93 ± 3·69	8·56 ± 3·19	0·42	9·01 ± 3·76	8·55 ± 3·15	0·32
Min. lumen area (mm^2)	4·49 ± 2·11	4·05 ± 1·89	0·09	4·48 ± 2·10	4·05 ± 1·89	0·10	4·42 ± 2·05	4·01 ± 1·84	0·15
Mean lumen area (mm^2)	6·69 ± 3·49	6·07 ± 2·21	0·04	6·52 ± 2·46	5·95 ± 2·20	0·05	6·62 ± 2·44	5·89 ± 2·18	0·03
Min. lumen diameter (mm)	2·33 ± 0·56	2·21 ± 0·53	0·11	2·32 ± 0·56	2·21 ± 0·53	0·12	2·31 ± 0·54	2·20 ± 0·52	0·17
Proj. min. lumen diameter (mm)	2·18 ± 0·52	2·08 ± 0·49	0·11	2·18 ± 0·52	2·08 ± 0·49	0·12	2·17 ± 0·51	2·07 ± 0·49	0·16
Stent length (mm)	26 ± 11	28 ± 14	0·14	26 ± 11	28 ± 14	0·13	27 ± 12	29 ± 14	0·34
Stent volume (mm^3)	255 ± 134	276 ± 179	0·31	256 ± 134	274 ± 175	0·36	266 ± 135	279 ± 180	0·52
Luminal volume (mm^3)	817 ± 91	172 ± 108	0·92	163 ± 93	165 ± 108	0·70	169 ± 92	167 ± 112	0·74
In-stent neo-intimal volume (mm^3)	84 ± 69	104 ± 92	0·064	93 ± 79	109 ± 96	0·16	97 ± 81	112 ± 96	0·21
In-stent obstruction volume (%)	32 ± 15	36 ± 16	0·034	36 ± 21	38 ± 18	0·32	36 ± 22	39 ± 18	0·31

Table 5 Six month follow-up quantitative angiographic results (intention-to-treat analysis)

	Placebo n=155	Trapidil n=148	*P*-value
Reference diameter (mm)	2·89 ± 0·39	2·81 ± 0·44	0·13
Minimal lumen diameter (mm)	1·74 ± 0·69	1·63 ± 0·61	0·17
Diameter stenosis (%)	40 ± 20	43 ± 17	0·32
Late loss (mm)	1·04 ± 0·56	1·12 ± 0·53	0·23
Loss index (mm)	0·59 ± 0·33	0·64 ± 0·38	0·28
Mean lumen diameter (mm)	2·50 ± 0·53	2·36 ± 0·55	0·04
Minimum luminal cross-sectional area (mm^2)	2·79 ± 1·67	2·51 ± 1·65	0·18
Mean luminal cross-sectional area (mm^2)	5·36 ± 2·29	5·03 ± 2·87	0·31
Restenosis rate (%)	24	31	0·24
No Corelab quantitative coronary angiography analysis	18 (12%)	20 (14%)	

Table 6 Major adverse cardiac events until 250 days (clinical ranking) intention-to-treat

	Placebo n=155	Trapidil n=148
Death	1 (1%)	3 (2%)
Myocardial infarction	3 (2%)	2 (1%)
Q wave	1 (1%)	1 (1%)
Non-Q wave	2 (1%)	1 (1%)
CABG	2 (1%)	2 (1%)
Urgent	2 (1%)	0
Elective	0	2 (1%)
Target lesion revascularization	25 (16%)	25 (17%)
Major adverse cardiac event free	124 (80%)	116 (78%)

Wilcoxon Rank-Sum test: $P=0·71$.

Table 7 Anginal status assessed prior either to the 6 months scheduled angiography or prior to any intercurrent angiography followed by an intervention

	Placebo n=155	Trapidil n=148
Anginal complaints	35 (24%)	41 (30%)
Missing information	11 (7%)	11 (7%)
No anginal complaints and/or signs of ischaemia	109 (76%)	96 (70%)

Wilcoxon Rank-Sum test: $P=0·29$.

probably compensates for the hyperplasia[14], so that late clinical results have been found to be generally satisfactory[3,21]. However, a recent experimental study demonstrated that the proliferative response after stenting is not only greater, but also more prolonged, compared to balloon angioplasty[22]. This implies that post-stent restenosis may paradoxically be too aggressive to be affected by oral trapidil, particularly in the case of a self-expanding stent, with its continued expansion after implantation[14], as confirmed by increased stent volume from post stenting (226 ± 135 mm^3, Table 3) to follow-up (256 ± 134 mm^3, Table 4). Undoubtedly, an effective antiproliferative agent would be expected to exert a particular benefit after Wallstent or other self-expanding stent placement, where the continued self-expansion might then achieve even more favourable late lumen expansion.

Use of a primary intravascular ultrasound volumetric end-point

This methodology, although relatively new, has been extensively validated in vitro and in vivo[12–14] and previously applied in a randomized clinical trial evaluating the effect of abciximab on late restenosis after stenting[10]. Although angiography remains the cornerstone of coronary intervention, it is evident that intravascular ultrasound provides superior information on the vessel wall, plaque and lumen for mechanistic evaluation of therapies. 3-D intravascular ultrasound provides precise measurement of the target of therapy, namely the bulk of the restenotic lesion. Further, use of hyperplastic volume as the end-point allows evaluation of the trial hypothesis with a smaller sample size than would be needed using the classical quantitative coronary angiography parameter (minimal lumen diameter (mm)). This methodology has now also been meticulously applied to evaluation of outcome after coronary brachytherapy, providing previously unattainable pathophysiological insights[23]. The drawback is that intravascular ultrasound examination, using current technology, is not always possible in patients with severe restenosis or total or subtotal occlusion, or not carried out for other reasons (Table 1), leading to potential bias if there is imbalance between the groups. Recognizing this limitation, an imputation algorithm was prospectively designed in this trial and was applied to 22 patients in the placebo group and 11 in the trapidil group, who had an analysable follow-up angiogram and post-stent angiogram and intravascular ultrasound. For completeness, all available data both with and without imputation, is provided for both the intention-to-treat and per-protocol population, showing consistently that trapidil provided no benefit in reducing restenosis.

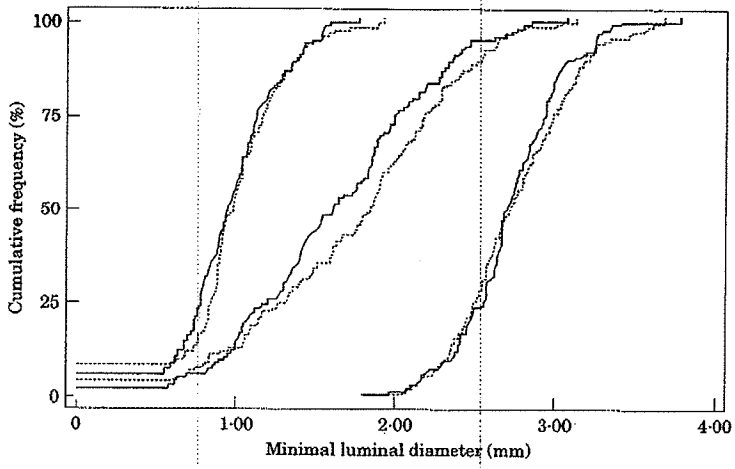

Figure 1 **Cumulative frequency distribution of minimal lumen diameter (mm) pre-, post- and follow-up. · · ·=placebo group; ——=trapidil group.**

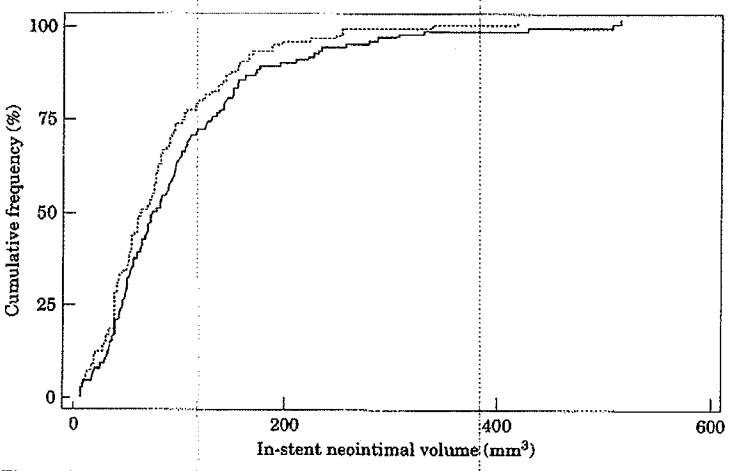

Figure 2 **Cumulative frequency distribution of in-stent neointimal volume. · · ·= placebo group; ——=trapidil group.**

It deserves to be pointed out that although an evaluable follow-up intravascular ultrasound rate of 78% may seem relatively low, the rate of follow-up intravascular ultrasound examination in those eligible for re-catheterization was 86%, and of the patients who underwent repeat catheterization 88% had an evaluable intravascular ultrasound. These figures compare very favourably with angiographic follow-up rates in most multicentre restenosis trials over the years, and reveal the increasing willingness of a diverse range of physicians to apply intravascular ultrasound during catheterization. Impending enhancement of catheter design (e.g. reduction in crossing profile, use of imaging guidewires) and intravascular ultrasound imaging and recording technology, can only lead to further improvements in the general applicability of intravascular ultrasound.

Limitations

Full and complete compliance with trial medication and complete angiographic and intravascular ultrasound follow-up would be ideal in every such randomized trial, but is for all the known reasons unattainable. At 1 month, compliance, defined as 90% of intake of medication, was 76% for trapidil and 83% for placebo, which is less than ideal but the lack of a major imbalance means this is unlikely to have affected the study outcome. Poor

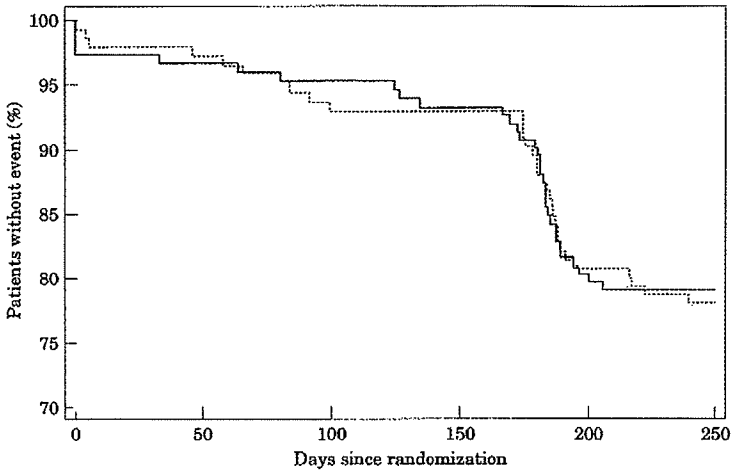

Figure 3 **Kaplan–Meier curves illustrating freedom from major adverse cardiac events during scheduled follow-up. · · · = placebo group; —— = trapidil group.**

compliance with trial medication, even if there had been a positive trial outcome, of course augurs very poorly for subsequent successful clinical application, since patients included in trials are inherently better motivated and receive closer instruction and follow-up than in routine clinical practice.

According to the statistical plan, a total of 240 evaluable patients were required in the intention-to-treat population analysis and finally 268 patients were analysed for the primary end-point, including 33 patients in whom the follow-up intravascular ultrasound data had to be imputed from the in-built pre-defined protocol. Although we believe the imputation protocol to be unbiased, objective and currently the best method of obtaining intravascular ultrasound measurements where acquisition was impossible, the imbalance between the groups here is unfortunate and cannot be explained as more than a chance occurrence. For the purpose of the primary hypothesis, as stated already, there is incontrovertibly no beneficial effect of trapidil on the late results, in fact a trend towards more hyperplasia, if anything, is evident. However, such a conclusion would also be inappropriate given the previously mentioned limitations.

Conclusion

Trapidil did not reduce restenosis after successful Wallstent implantation, measured by three-dimensional intravascular ultrasound neointimal volume, or by angiographic indices or clinical events and is thus not indicated for this purpose. Follow-up intravascular ultrasound examination was found to be eminently applicable in the multicentre context and automated three-dimensional measurement presents a promising advancement for interventional trials. Further improvements in intravascular ultrasound catheter technology will be required to increase a successful application rate at follow-up catheterization.

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Appendix A

Members of the TRAPIST study committee

Steering Committee: P. W. Serruys, MD, Ph.D. (chair), A. Mignot, MD, R. Ott, MD, G.-A. van Es, MD, A. A. van den Bos, MD, B. Meier, MD, Y. Teunissen, Ph.D., P. de Feyter, MD PhD, C. van de Zwaan, MD, C. Kawai, MD, D. L. Clement. *Data Safety Monitoring Committee*: C. Kawai, MD (chair), J. Tijssen, Ph.D., P. de Jaegere, MD PhD. *Clinical Event Committee*: C. van de Zwaan, MD (chair), P. Klootwijk, MD, P. van der Meer, MD PhD. *IVUS-Angiographic Committee*: P. De Feyter, MD PhD (chair), T. Slagboom, MD, C. Vrints, MD. *Statistical analyses*: R. Melkert, MD, C. C. M. Disco, M.Sc.

Appendix B

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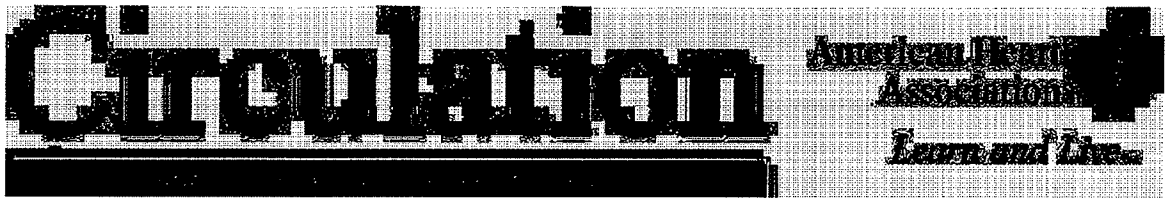
Italy: Centro Cuore Colombus, Milan: A. Colombo, A. Amato.

Inter Partes Reexamination No. 95/001,102
Declaration of Campbell Rogers, M.D.
Exhibit 102



Vascular Responses at Proximal and Distal Edges of Paclitaxel-Eluting Stents: Serial Intravascular Ultrasound Analysis From the TAXUS II Trial

Patrick W. Serruys, Muzaffer Degertekin, Kengo Tanabe, Mary E. Russell, Giulio Guagliumi, John Webb, Jaap Hamburger, Wolfgang Rutsch, Christoph Kaiser, Robert Whitbourn, Edoardo Camenzind, Ian Meredith, François Reeves, Christoph Nienaber, Edouard Benit, Clemens Disco, Jörg Koglin, Antonio Colombo and for the TAXUS II Study Group

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Vascular Responses at Proximal and Distal Edges of Paclitaxel-Eluting Stents

Serial Intravascular Ultrasound Analysis From the TAXUS II Trial

Patrick W. Serruys, MD; Muzaffer Degertekin, MD; Kengo Tanabe, MD; Mary E. Russell, MD; Giulio Guagliumi, MD; John Webb, MD; Jaap Hamburger, MD; Wolfgang Rutsch, MD; Christoph Kaiser, MD; Robert Whitbourn, MD; Edoardo Camenzind, MD; Ian Meredith, MD; François Reeves, MD; Christoph Nienaber, MD; Edouard Benit, MD; Clemens Disco, MSc; Jörg Koglin, MD; Antonio Colombo, MD; for the TAXUS II Study Group

Background—On the basis of brachytherapy experience, edge stenosis has been raised as a potential limitation for drug-eluting stents. We used serial intravascular ultrasound (IVUS) to prospectively analyze vessel responses in adjacent reference segments after implantation of polymer-controlled paclitaxel-eluting stents.

Methods and Results—TAXUS II was a randomized, double-blind trial with 2 consecutive patient cohorts that compared slow-release (SR) and moderate-release (MR) paclitaxel-eluting stents with control bare metal stents (BMS). By protocol, all patients had postprocedure and 6-month follow-up IVUS. Quantitative IVUS analysis was performed by an independent core laboratory, blinded to treatment allocation, in 5-mm vessel segments immediately proximal and distal to the stent. Serial IVUS was available for 106 SR, 107 MR, and 214 BMS patients. For all 3 groups, a significant decrease in proximal-edge lumen area was observed at 6 months. The decrease was comparable (by ANOVA, $P=0.194$) for patients in the SR (-0.54 ± 2.1 mm^2) and MR (-0.88 ± 1.9 mm^2) groups compared with the BMS (-1.02 ± 1.9 mm^2) group. For the distal edge, a significant decrease in lumen area was only observed with BMS (-0.91 ± 2.0 mm^2, $P<0.0001$); this decrease was significantly attenuated with SR (0.08 ± 2.0 mm^2) and MR (-0.19 ± 1.7 mm^2) stents ($P<0.0001$ by ANOVA). Negative vessel remodeling was observed at the proximal (-0.48 ± 2.2 mm^2, $P=0.011$) but not the distal edges of BMS and at neither edge of SR or MR stents.

Conclusions—The marked reduction in in-stent restenosis with SR or MR stents is not associated with increased edge stenosis at 6-month follow-up IVUS. In fact, compared with BMS, there is instead a significant reduction in late lumen loss at the distal edge with TAXUS stents. **(*Circulation*. 2004;109:627-633.)**

Key Words: angioplasty ■ drugs ■ stents ■ ultrasonics

In-stent restenosis related to neointimal hyperplasia after stent implantation remains a major clinical problem.[1,2] Over the past decade, both systemic pharmacological and novel mechanical treatment strategies to prevent in-stent neointimal hyperplasia have been unsuccessful.[3–5] Only intracoronary radiation therapy has emerged as a promising modality to attenuate the neointimal hyperplasia after stent placement.[6,7] However, initial enthusiasm in the use of radioactive stents has been limited by the occurrence of stenosis in the segments adjacent to the proximal and distal edge of the stent (so-called edge stenosis).[8,9]

Recently, stent-based local drug delivery with a number of pharmacological agents has been demonstrated to reduce in-stent neointimal hyperplasia. Randomized clinical safety and feasibility trials with sirolimus- and paclitaxel-eluting stents have shown very promising results, with prevention of in-stent restenosis in de novo coronary and in-stent restenosis lesions.[10,11] However, initial enthusiasm has been tempered by concerns regarding potential untoward effects. Among these concerns is the possibility that edge effects, analogous to those observed with radioactive stents and after intravascular brachytherapy, might limit the effectiveness of drug-

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eluting stents. In the initial trials with sirolimus-eluting stents (SES), the FIM[12] and RAVEL (RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent)[11] trials, no edge effect was reported. In the SIRIUS trial (a multicenter study of the SIRolImUS-eluting Bx-velocity stent in the treatment of patients with de novo coronary artery lesions), which evaluated SES in a more complex population than RAVEL, a higher rate of significant (>50% diameter stenosis) stenosis was observed at the proximal edge of the SES than at either the stented region or its distal edge (M.B. Leon, MD, unpublished data, 2002). These observations have prompted renewed concern regarding the issue of "edge" stenosis with drug-eluting stents.

In the TAXUS I trial,[10] no edge restenosis was seen with a slow-release (SR) paclitaxel formulation; however, this was a feasibility study that included only 61 patients. The TAXUS II trial compared 2 consecutive cohorts (SR and moderate-release [MR] polymer formulations of paclitaxel-eluting stents) with control bare metal stents (BMS) and mandated serial intravascular ultrasound (IVUS) examinations, which provided a unique opportunity to obtain detailed information on the outcome at vessel segments adjacent to paclitaxel-eluting stents.

Methods

Patient Selection

TAXUS II was a randomized, double-blind, controlled trial conducted in 38 centers. Patients were eligible for inclusion if (1) they had stable or unstable angina pectoris or documented silent ischemia and (2) they were scheduled for treatment of a single significant (>50% stenosis on visual assessment) de novo target lesion in a native coronary artery that could be treated with a single stent (3.0 or 3.5 mm in diameter and 15 mm long). Major exclusion criteria were total vessel occlusion (TIMI grade 0 to 1) before intervention, intervention for evolving myocardial infarction, significant (>50% diameter stenosis) unprotected left main coronary artery stenosis, ostial location of the target lesion, lesion calcification that precluded successful predilation, angiographic evidence of thrombus within the target lesion, left ventricular ejection fraction <30%, or intolerance to aspirin or clopidogrel. The current IVUS substudy included patients who received 1 study stent and underwent serial IVUS examination after the procedure and at 6-month follow-up. The study was reviewed and approved by each participating institution's Ethics Review Committee, and written informed consent was obtained from all patients.

TAXUS (Paclitaxel-Eluting) Stent System

The stent used in the present study was the NIR Conformer stent (Boston Scientific Corporation and Medinol Ltd). The control BMS was an uncoated steel stent (NIRx, Boston Scientific). The TAXUS NIRx stent was coated with proprietary polymer (Translute) designed to control paclitaxel release with an initial burst phase for ≈10 days.[13] All TAXUS stents were coated with paclitaxel (total loaded dose of 1.0 $\mu g/mm^2$). Two paclitaxel-eluting release formulations were evaluated (SR and MR), with an 8-fold higher release rate for the MR formulation in the first 48 hours. All stents were 15 mm long and 3.0 or 3.5 mm in diameter on 20-mm balloon delivery catheters.

Study Design and Procedure

To evaluate the safety and performance of the TAXUS NIRx stent, patients in 2 sequential cohorts were randomized (1:1 ratio), after successful predilation, to receive either the TAXUS or a control NIRx BMS. In cohort 1, patients were randomized to SR or BMS. In cohort 2, patients were randomized to MR or BMS.

Stents were deployed at 10 to 16 atm, and postdilation was performed as necessary to achieve a residual stenosis below 20%. Heparin was administered in intravenous boluses to maintain an activated clotting time >250 seconds for the duration of the procedure and was discontinued within 12 hours. Administration of aspirin (at least 100 mg) was begun 12 hours before the procedure and was continued indefinitely. A loading dose of clopidogrel (300 mg) was administered, preferably 48 hours before the procedure, followed by 75 mg once daily for 6 months.

Quantitative IVUS and Angiographic Analysis

Serial IVUS (after the procedure and at 6-month follow-up) procedures were performed after administration of 200 μg of intracoronary nitroglycerin, with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotapes, and images were digitized for analysis. A computer-based contour detection was performed with QURAD QCU analysis software (Curad BV, Wijk Bij Duurstede) for 3D reconstruction, as described elsewhere.[14] In the quantitative analysis of the edge segments, the vessel segments beginning 5 mm distal to and extending 5 mm proximal to the stented segment were examined. When calcification with acoustic shadowing or side branches were located in the 5-mm segment proximal or distal to the stent, the external elastic membrane contours were not analyzable, which reduced the length of analysis to <5 mm in these segments.

To clarify the mechanism of possible edge responses to drug elution at different distances from the stent struts, we also performed IVUS analysis for each 1-mm subsegment and for the entire 5-mm edge segments. Therefore, both proximal and distal vessel segments were further divided into 1-mm subsegments and numbered from 1 (nearest the stent) to 5. For each subsegment, vessel, lumen, and plaque areas were calculated from each available cross-sectional slice (up to 50 slices/mm) obtained after digitization of the videotapes and were expressed as mean values. Area changes (Δ values) for each measurement were calculated as follow-up minus postprocedure value. To eliminate the influence of vessel size, percent change [(Δ area/postprocedure area×100] was also calculated. The quantitative ultrasound and coronary angiographic analyses were performed by an independent core laboratory that remains blind to treatment allocation during follow-up (Cardialysis).

Statistical Analysis

The BMS groups of the 2 cohorts were combined because the baseline and 6-month follow-up data showed no significant differences, as described previously.[15] Therefore, 3 groups are reported in the present study: the combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are given as percentages and were tested with Fisher's exact test. Continuous variables are expressed as mean±SD. Changes for each measurement were calculated as follow-up minus postprocedure values. When the 3 groups were compared, overall probability values were derived from 1-way ANOVA. Comparisons between postprocedure and 6-month follow-up values were performed with a 2-tailed paired t test, whereas comparisons between 2 groups were performed with Fisher's least significant difference test. A value of $P<0.05$ was considered statistically significant.

Results

Overall, 536 patients, (270 BMS, 135 MR, and 131 SR) were randomized in the TAXUS II trial. IVUS edge analysis could not be performed either in part or in all of the predefined 5-mm edge segments in some patients (n=162) for 1 or more of the following reasons: incomplete image acquisition (23%), inadequate image quality (9%), or the presence of major side branches (68%). Of the 536 patients, 427 with 1 stent and paired IVUS edge analyses (214 BMS, 106 SR, and 107 MR) entered in this substudy. Baseline clinical, demo-

TABLE 1. Baseline Clinical and Procedural Characteristics

Characteristics	Combined Control (n=214)	Taxus SR (n=106)	Taxus MR (n=107)
Age, y	59.9±9.61	61.9±10.4	59.6±10.3
Male	78.5	69.8	72.9
Current smoker	27.6	20.8	22.4
Diabetes mellitus	14.5	11.3	15.0
Hypertension	61.2	61.3	59.8
Hypercholesterolemia	73.7	81.1	77.6
Unstable angina	34.3	34.0	29.2
Prior MI	45.8	39.6	37.4
Target-lesion vessel			
LAD	46.7	39.6	42.1
LCA	14.5	19.8	22.4
RCA	38.8	40.6	35.5
RVD before intervention, mm	2.73±0.44	2.78±0.44	2.73±0.45
Maximum balloon:artery ratio	1.1±0.2	1.1±0.2	1.1±0.2
Maximum inflation pressure, atm	12.4±2.7	12.7±2.7	12.2±2.8
Quantitative angiography at follow-up			
Proximal edge late loss, mm	0.33±0.40	0.18±0.33*	0.16±0.37*
Binary restenosis	2.8 (6/214)	1.9 (2/106)	2.8 (3/107)
Distal edge late loss, mm	0.20±0.38	0.07±0.32*	0.05±0.31*
Binary restenosis	2.3 (5/214)	1.9 (2/106)	0.9 (1/107)
In-stent late loss, mm	0.74±0.44	0.30±0.30*	0.25±0.35*
Binary restenosis	15.9 (34/214)	0.9 (1/106)	0.9 (1/107)

MI indicates myocardial infarction; LAD, left anterior descending artery; LCA, left coronary artery; RCA, right coronary artery; and RVD, reference vessel diameter.

Values are % (count/sample size) or mean±SD.

*$P<0.05$ vs control group.

graphic, and angiographic characteristics were similar among BMS, SR, and MR groups (Table 1). Serial IVUS was available for the proximal edge in 161 BMS, 84 SR, and 84 MR patients and for the distal edge in 191 BMS, 97 SR, and 98 MR patients.

Mean Changes Within the Entire 5-mm Section at Proximal and Distal Edges

Mean vessel area, plaque area, and lumen area of the entire 5-mm edge segment (proximal and distal) were comparable, with no statistically significant differences between the 3 groups immediately after the procedure (baseline) or during the 6-month follow-up (Tables 2 and 3). At the proximal edge, only the control group showed significant constrictive vascular remodeling, with a decrease in mean vessel area of the entire proximal edge from baseline to follow-up ($P=0.011$), whereas neither the SR or MR groups showed any differences (SR, $P=0.689$; MR, $P=07.82$). With a comparably significant increase in mean plaque area in all 3 groups, this still translated into a significant decrease in mean lumen area in all 3 groups (Figure 1).

At the distal edge, the mean plaque and vessel area remained comparable among all 3 groups. However, the lumen area of the entire distal edge differed significantly between control (7.6±2.8 mm^2) and SR (8.4±2.9 mm^2; $P=0.0185$) groups. From baseline to follow-up, the vessel area of the distal edge decreased in the control group, whereas it increased in the SR and MR groups. With a comparable increase in mean plaque area in all 3 groups, this translated into a significant decrease in mean lumen area in the control group compared with a stable lumen area in both the SR and MR groups (Figure 1).

Analyses of the vascular response at the proximal or distal edges of the stent in the 3 groups (BMS, MR, and SR) were also performed for patients who underwent postdilation of the stent and for those who exhibited an early or late malapposition of the stent. No level of statistical significance could be detected between groups with and without postdilation, with or without malapposition. Changes in EEM volume and area, lumen volume and area, and plaque volume and area at the proximal and distal edges of the stent were not statistically different between the MR and SR groups.

Subsegmental Analysis of Longitudinal Changes at 5-mm Edge Segment of Proximal and Distal Edges

In a per-segment analysis that analyzed 5 consecutive 1-mm segments adjacent to the stent, vascular remodeling proximal to the SR and MR stents differed within the first 1-mm subsegment. Although vessel area, plaque area, and lumen area did not differ between the different segments and different groups at baseline, positive vascular remodeling, reflected by an increase in vessel area, was more pronounced

TABLE 2. Serial IVUS Results of Proximal Edge

Proximal Edge	Control (BMS) (n=161)	Taxus-SR (n=82)	Taxus-MR (n=85)	*P* Overall
Vessel area, mm²				
Postprocedure	16.9±4.3	16.8±4.8	16.6±4.0	0.82
6-Month follow-up	16.4±4.2	16.9±4.5	16.5±4.0	0.70
P	<0.01	0.689	0.782	
Plaque area, mm²				
Postprocedure	7.7±2.9	7.6±2.9	7.5±2.7	0.81
6-Month follow-up	8.2±2.9	8.2±2.9	8.3±2.9	0.97
P	<0.0005	<0.0005	<0.0005	
Lumen area, mm²				
Postprocedure	9.2±3.0	9.2±2.9	9.1±2.6	0.93
6-Month follow-up	8.3±2.9	8.7±3.0	8.2±2.4	0.47
P	<0.0001	<0.02	<0.0001	

Numbers are mean±SD.
P=NS for MR vs SR. Overall *P* values are from 1-way ANOVA for continuous variables.

within this first subsegment in the SR and MR groups than in the control group ($P=0.0052$; Figure 2). Together with a comparable increase in plaque area in all 3 groups, this resulted in significantly less lumen area loss in the SR and MR groups (-0.55 ± 2.1 and -0.78 ± 2.0 mm²) than in the control group (-1.42 ± 2.2 mm², $P=0.0055$). Beyond the first proximal segment, the change in lumen area, plaque area, and vessel area did not differ significantly between the SR, MR, and control groups (Figure 2).

At the distal edge, the beneficial effect of SR and MR stents on change in lumen area was evident on all 5 1-mm subsegments distal to the stent. The comparable decrease in plaque area in the first 2 subsegments in all 3 groups was balanced in the SR and MR groups by positive vascular remodeling, reflected by an increase in vessel size. This resulted in stable lumen area in all subsegments in both SR and MR patients, whereas the control group exhibited a significant decrease along all 5 subsegments of the distal edge ($P<0.001$ versus SR and MR).

Difference Between Proximal and Distal Edges

There were no significant differences between proximal and distal edges with respect to percentage changes in either vessel or plaque area among groups. However, although there were no significant differences in percent lumen area change between proximal and distal edges with the BMS (−9.6% versus −8.9%, respectively, $P=0.91$), for TAXUS stents, a significant decrease in lumen area at the proximal compared with the distal edges was seen in both the MR (−7.6% versus 0.04%, respectively, $P=0.01$) and SR (−4.4% versus 3.1%, respectively, $P=0.03$) groups.

Discussion

In the present study, we evaluated the behavior of vessel segments adjacent to polymer-controlled SR and MR paclitaxel-eluting stents (TAXUS) by serial IVUS. The major finding of the study was that the use of TAXUS stents was not associated with a significant increase in edge stenosis compared with BMS. Indeed, the luminal area at the distal edge of

TABLE 3. Serial IVUS Results of Distal Edge

Distal Edge	Control (BMS) (n=187)	Taxus-SR (n=94)	Taxus-MR (n=96)	*P* Overall
Vessel area, mm²				
Postprocedure	14.7±4.5	14.4±4.3	14.1±4.3	0.54
6-Month follow-up	14.5±4.3	14.8±4.5	14.4±4.1	0.74
P	0.115	0.064	0.103	
Plaque area, mm²				
Postprocedure	6.3±3.1	6.1±2.8	5.8±2.7	0.45
6-Month follow-up	6.9±3.0	6.4±2.7	6.3±2.7	0.14
P	<0.0001	0.073	<0.02	
Lumen area, mm²				
Postprocedure	8.4±2.9	8.4±2.7	8.3±3.0	0.88
6-Month follow-up	7.6±2.8	8.4±2.9	8.0±2.8	0.05
P	<0.0001	0.767	0.190	

Numbers are mean±SD.
P=NS for MR vs SR. Overall *P* values are from 1-way ANOVA for continuous variables.

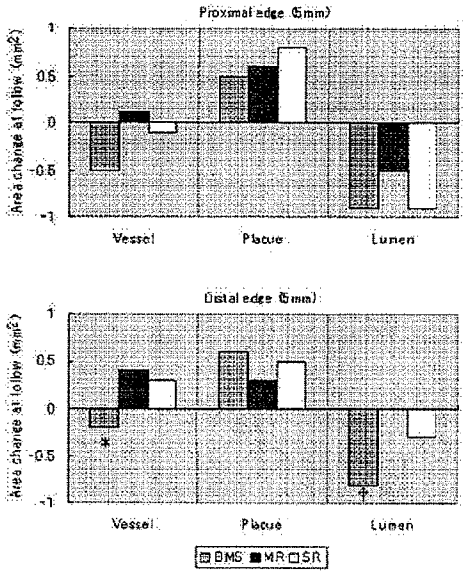

Figure 1. Averaged area changes (follow-up minus postprocedure) for entire 5-mm edge segment in lumen, plaque, and vessel at proximal and distal edge segments. *$P<0.05$, †$P<0.0005$ by 1-way ANOVA.

TAXUS stents was significantly greater than that of BMS at follow-up owing to the occurrence of positive vascular remodeling.

Edge Effects and Restenosis

The inevitable arterial injury due to balloon deployment of a stent coupled with the presence of a metallic foreign body causes inflammatory and proliferative responses.[16] Animal studies have shown that this results in neointimal hyperplasia not only within the stent but also at the edges, in the adjacent reference segments.[17] In the present study, the correlations between intrastent neointimal area and change in proximal/distal plaque area were investigated separately for all 3 groups. The statistical analysis showed that the intrastent neointimal area was correlated with the distal plaque area in each group and correlated with the proximal plaque area in the MR and control groups but failed to be significant in the SR group. These relationships would suggest that the vascular responses at the proximal and distal edges reflect a global responsiveness of the vessel to the degree of neointimal inhibition induced by the drug with both eluting formulations.

The concerns regarding edge effects with a drug-eluting stent reflect potential similarities between the effects of radioactive stents and those of drug-eluting stents, such as local inhibition of neointimal growth and delayed endothelial healing.[18] In patients treated with radioactive stents, edge stenosis has proved to be an important clinical problem, occurring in 30% of patients.[8,19] TAXUS II confirmed that no edge effect greater than that found with a BMS occurs with either MR or SR paclitaxel-eluting stents. As reported previously, the term "edge effect" is used to connote an effect greater than would be seen with BMS.[8,19] In fact, there was a slight but nonsignificant decrease in edge stenosis compared with BMS. Edge stenosis (diameter stenosis >50%) rates for BMS were 3.4% (proximal) and 3.1% (distal), whereas for the SR and MR groups, the rates were 1.6% and 2.3% at the proximal and distal edges, respectively.

In sirolimus-eluting stent trials, no edge stenosis was reported in the FIM and RAVEL trials. However, in the SIRIUS trial, which included patients with more complex lesions than either the RAVEL[11] or TAXUS II trials, edge stenoses, which were more frequently observed at the proximal than at the distal edges and in smaller (<3 mm) vessels, occurred in 5.8% of patients, although the in-stent restenosis rate (3.2%) was similar to that in TAXUS II.

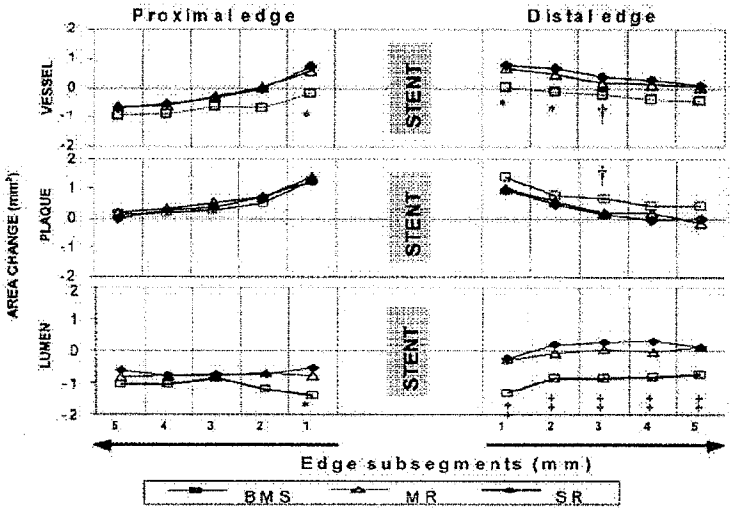

Figure 2. Every 1-mm mean area change (follow-up minus postprocedure) in lumen, plaque, and vessel at proximal and distal edge subsegments. *$P<0.05$, ‡$P<0.01$ by 1-way ANOVA; †$P=0.0052$, BMS vs SR.

Remodeling in Segments Adjacent to the Stent: Insights From IVUS

Previous serial IVUS studies reported that significant lumen loss occurs at the proximal segment after BMS implantation. However, there is controversy as to the mechanism(s) involved. Hoffmann et al[2] and Weissman et al[20] reported that this luminal loss was predominantly related to negative remodeling, whereas Mudra et al[1] suggested that it was related to an increase in plaque burden. In the present study, both BMS and TAXUS stents showed a significant decrease in lumen area in the proximal reference segment at follow-up. Whereas this was due to both negative remodeling and plaque increase in BMS, it was related to plaque increase without significant vessel remodeling in TAXUS stents. Subsegment analysis for BMS demonstrated that in the 2 mm proximal to the stent, lumen loss was exclusively due to plaque increase, whereas more proximally, it reflected both plaque increase and negative remodeling. With TAXUS stents, lumen loss was significantly less than for BMS. This was due to the fact that plaque increase was compensated by positive remodeling. However, there was no statistical argument to suggest the superiority of one eluting formulation over the other.

Previous studies regarding distal edge behavior in BMS have produced conflicting results. Mudra et al[1] reported no significant lumen loss or negative remodeling in the 3 mm distal to BMS edges, whereas Weissman et al[20] reported discordant results showing significant lumen loss throughout the distal reference segment. In the present study, BMS demonstrated significant lumen loss in the distal reference segment without negative remodeling. In detailed subsegment analyses, we demonstrated that lumen loss in the 2 mm distal to the stent edge was related to plaque increase, in accordance with the results of Weisman et al.[20]

In contrast to BMS, TAXUS stents were associated with a beneficial effect on the distal reference segment, where no significant lumen narrowing was observed at follow-up. The subsegment analysis showed that this reflects the fact that positive vascular remodeling compensated for the increase in plaque burden in the reference segment immediately (<2 mm) adjacent to the stent. Possible reasons for the beneficial effects of the drug at the distal edge and for the difference between the behavior of proximal and distal edge segments include higher downstream concentrations of the drug or the relatively smaller distal vessel size.

Previous Drug-Eluting Stent Trials

The IVUS findings in TAXUS II are consistent both with the quantitative angiographic results reported in TAXUS I and II (Table 1) and with the results of the sirolimus-eluting stent trials, all of which showed a decrease in lumen loss, compared with BMS, at the distal edge of the stent. Only 2 studies (Honda et al,[21] and the ASian Paclitaxel-Eluting Stent Clinical Trial [ASPECT][22]) reported serial IVUS edge analysis in small numbers of patients. In the ASPECT study,[22] there were no significant changes at either edge, whereas in the study by Honda et al,[21] there was significant lumen loss at the distal edge. This observation in the latter study is contrary to the findings of the present study. We have recently evaluated edge responses after SES by serial IVUS in a subset of RAVEL and FIM patients and found no significant changes between implantation and follow-up at either proximal or distal edges in any of the parameters studied.

Study Limitations

Patients included in the present study had simple de novo coronary lesion and low-risk profiles, which reflects the inclusion criteria of the TAXUS II trial. The study results cannot be extrapolated to more complex coronary lesions. Furthermore, the follow-up period is relatively short, and no conclusions can be drawn regarding ultimate long-term behavior at the stent edges.

Conclusions

These results suggest that concerns regarding edge stenosis with TAXUS-eluting stents are unfounded. Indeed, compared with BMS, TAXUS stents appear to have a significant protective effect against distal edge "restenosis" compared with BMS. A similar trend was noted for the proximal edge. These effects were observed with both SR and MR formulations.

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REVIEW ARTICLE

Drug-Eluting Stents
Preventing Restenosis

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Abstract: The introduction of percutaneous transluminal coronary angioplasty has revolutionized the field of cardiology by providing patients with coronary artery disease immediate and effective therapy. Overshadowing the early success of angioplasty was the high rate of angiographic restenosis and recurrent symptoms at 6 months. The use of stents reduced the incidence of restenosis; however, the rise in the number of patients undergoing percutaneous interventions produced a new problem of restenosis occurring within the stent: in-stent restenosis (ISR). Mechanical approaches, including directional and rotational atherectomy and systemic pharmacotherapy, have failed to demonstrate a reduction in ISR in randomized clinical trials. Intravascular brachytherapy is currently the only approved therapy for ISR, although this treatment has numerous unresolved questions and is not effective in a large percent of patients. Drug-eluting stents have reduced the incidence of restenosis by providing localized therapy to the targeted lesion without systemic toxicity. The purpose of this review is to synthesize data from major clinical trials involving the 2 most successful agents used in the prevention of restenosis: sirolimus and paclitaxel. The cellular and molecular mechanisms of both ISR and restenosis postangioplasty derived from animal models will be introduced. Second, an overview of 3 alternate interventions that attempt to reduce the rates of restenosis is presented. Finally, the major randomized, controlled trials involving sirolimus and paclitaxel are described, and their clinical implications and use as a possible solution in the prevention of restenosis is discussed.

Key Words: stents, sirolimus, restenosis, percutaneous transluminal coronary angioplasty, paclitaxel

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Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States, accounting for 1 of every 5 deaths.[1] According to the American College of Cardiology, 13 million Americans are currently living with CAD. In 2001, it was estimated that more than 1 million individuals experienced a new or recurrent coronary attack. In addition, CAD accounted for approximately $130 billion in total healthcare expenditures.[1]

Percutaneous transluminal coronary angioplasty (PTCA), first preformed in 1977 by Andreas Gruentzig, has revolutionized therapy for CAD. Since then, the field of interventional cardiology has witnessed vast improvement in techniques and an increase in research designed to eliminate some of the limitations associated with PTCA.[2,3] Restenosis, historically occurring in approximately 30% to 60% of patients within the first 6 months, is the Achilles heel of PTCA.[4–6] Restenosis is defined as an arterial healing response after injury involving vascular elastic recoil, neointimal proliferation, and negative remodeling.[2,3,7] Postangioplasty restenosis primarily results from negative remodeling with contraction formation, which accounts for more than 60% of late luminal loss.[4,7,8] Stenting has effectively reduced the restenosis rates to approximately 15% to 30% by functioning as a mechanical scaffold that eliminates elastic recoil and negative remodeling.[4,5,9] The drastic rise in the use of stents identified a new problem with PTCA: restenosis occurring within the stent. In-stent restenosis (ISR) is defined as lumen diameter loss of greater than 50% within the stent. Abnormal coronary reserve can be demonstrated in the vessel once the diameter stenosis exceeds 50%.[10] The only U.S. Food and Drug Administration-approved treatment of ISR is intracoronary radiation. Given the prevalence of CAD and the large volume of individuals who will undergo percutaneous coronary interventions, ISR could continue to be a major problem faced by interventional cardiologists.

The purpose of this review is to discuss the use of drug-eluting stents (DES) in the prevention of restenosis.

PATHOGENESIS OF RESTENOSIS

Postangioplasty Restenosis

The comparable size of their coronary arteries as well as their similar response to injury makes the porcine coronaries an effective model to demonstrate the pathophysiology and histopathology of restenosis.[11] The pathogenesis of restenosis, which is distinct from atherosclerotic plaque formation, is similar to wound healing. The process can be divided into 1) elastic recoil, 2) neointimal hyperplasia, and 3) negative vascular remodeling.[2,3,7] *Elastic recoil* is an acute

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process that is observed within a few minutes after balloon deflation, resulting in a mechanical collapse of the vessel wall. The large quantity of elastic fibers within the tunica media increases the inward recoil force on balloon inflation, causing acute luminal collapse after deflation. The recoil force can result in up to 50% loss of the cross-sectional area and a 33% loss in luminal diameter.[12] Neointimal formation and negative remodeling result from direct trauma to the artery.

Neointimal Formation

Balloon inflation increases intravascular pressure, often causing rupture of the medial layer at the junction between the normal segment and the atherosclerotic plaque, leading to dissection through the tunica media, exposing the subendothelial components.[13] The endothelial denudation leads to the loss of antithrombotic factors such as nitric oxide, prostaglandin, and tissue plasminogen activator, and promotes platelet adhesion and aggregation. Platelets bound to fibrin release cytokines such as platelet-derived growth factor (PDGF), thromboxane A2, and adenosine diphosphate (ADP) that signal further platelet aggregation and the formation of thrombus.[13,14]

PDGF, transforming growth factor, and epidermal growth factor are cytokines released by the platelets that function as mitogens and chemotaxic agents for vascular smooth muscle cells (VSMC) and macrophages.[15,16] The macrophages release PDGF and interleukin-6, which further stimulate VSMC. The VSMC normally reside in the tunica media in their quiescent state.[15,16] On injury, the release of these mediators leads VSMC to phenotypically change into myofibroblasts with synthetic, secretory, proliferative, and migratory function. These cells exit the G_0 quiescent phase, migrate into the site of injury, and undergo mitosis. In addition, endothelial denudation leads to the loss of heparin-like glycosaminoglycans that normally inhibit the growth of VSMC.[17]

Intracellular signaling pathways that govern these changes have been studied in great detail by Indolfi et al,[18] who has demonstrated that the 2 major cascades governing the function of VSMC are the tyrosine kinase cascade and the cyclic–AMP pathway. Growth factors bind to the receptors and activate tyrosine kinase that leads to a phosphorylation cascade, eventually activating *ras*. *Ras* stimulates *raf* to activate mitogen-activated protein kinase kinase, culminating in intranuclear activation of transcription factors that induce proliferation and migration of VSMC.[18] The cyclic–AMP pathway leads to the activation of protein kinase A (PKA), which phosphorylates and activates the transcription factor cAMP-responsive element-binding protein.[18] In addition, protein kinase A phosphorylates *raf*, inhibiting the other major pathway involved in the activation of VSMC.[18] In vitro and in vivo studies demonstrate that the inactivation of *ras* and the activation of the cyclic–AMP pathway leads to a greater than 50% reduction in neointimal formation at 14 days postballoon injury in rat carotid arteries.[18–20]

The progression of G_0 to G_1 is regulated by a cyclin-dependent kinase, particularly cyclin D-CDK and cyclin E-CDK-2.[18] The presence of endogenous inhibitors of cyclin dependent kinase, such as $p21^{cip1}$, $p27^{kip1}$, and INK4 families regulate the process of entering G_1 and keep VSMC in the G_0 phase.[18] Vascular inflammation and injury decreases the level of $p27^{kip1}$ that causes quiescent cells to resume cell division. Activation of cAMP leads to an increase in $p27^{kip1}$ forcing the proliferating cells to exit the cell cycle.[18] The complex interplay of intracellular signals leads to the conversion of VSMC to myofibroblasts and migration to the site of injury. Histologic analysis in the porcine model demonstrates that these actin (+) cells colonize the residual thrombus, forming a cap across the thrombus and proliferating toward the tunica media. The myofibroblasts then degrade the thrombus and replace it with extracellular matrix, leading to the formation of the neointimal mass.[14] The amount of neointima produced is determined by the degree of inflammation generated during vascular injury.[21]

Negative Remodeling

Remodeling is a change in arterial size after vascular injury that stems from the ability of the artery to enlarge or contract.[7] The process of negative remodeling can be observed 1 to 6 months postangioplasty and accounts for approximately 60% to 65% of luminal loss observed by intravascular ultrasound (IVUS).[7,8] Wilcox et al used antibodies against alpha-smooth muscle actin, myosin, and desmin to demonstrate the proliferation of myofibroblasts in the neointima and the adventitia.[22] The adventitia is the site with the greatest expression of PDGF and PDGF receptors, which are mediators critical in attracting myofibroblasts to the site of injury.[13,22] On injury to the vessel, inflammatory cells stimulate conversion of adventitial fibroblasts to myofibroblasts that express alpha-smooth muscle actin and secrete extracellular matrix, leading to constriction of the vessel and the formation of a fibrotic scar within the adventitia surrounding the site of injury.[22] The combination of elastic recoil, neointimal formation, and negative remodeling accounts for the high restenosis rates after balloon angioplasty.

In-Stent Restenosis

Clinical trials comparing balloon angioplasty versus stenting demonstrate a reduction in restenosis rates with the use of stents. The introduction of a stent eliminates elastic recoil. Stenting provides a mechanical scaffold that prevents the recoil force from causing mechanical collapse of the lumen.[23] Contrary to initial expectations, studies have demonstrated that stent implantation promotes the development of neointimal hyperplasia.[24] Hoffman et al compared stented and nonstented lesions using serial IVUS studies, confirming the observation that the main mechanism of ISR is the result of neointimal hyperplasia rather than negative remodeling.[25] The late lumen loss is actually greater with bare metal stents than with balloon dilation alone. However, the initial gain in lumen diameter is so much greater with stents that this overcomes the neointimal production to yield a lower restenosis rate.[23]

The neointimal formation that occurs in ISR is similar to that after balloon angioplasty. The exaggerated response seen with stenting occurs secondary to the increase of vessel injury and inflammation. Kornowski et al, using a porcine model, demonstrated that an increase in vessel injury or vascular inflammation results in an increase in neointimal

formation.[26] Pigs in which the stent struts perforated the internal elastic lamina and external elastic lamina had greater histologic evidence of inflammatory response and subsequently a larger volume of neointimal formation.[26] Other contributing factors to increased inflammatory response may stem from the increased balloon inflation required to place the stent or the irritating reaction to the stent material. Contact allergy to metals, including nickel and molybdenum, may account for the elevated inflammatory response observed with stents. Bare metal stents (BMS) slowly elute metal ions that may stimulate a delayed-type hypersensitivity response within the stented vessel.[27] A study was conducted in Germany on 131 patients who, after stent implantation, underwent cutaneous patch testing to investigate the association of nickel and molybdenum hypersensitivity with ISR. All patients ($n = 10$) with a positive test result had restenosis ($P = 0.03$) requiring target vessel revascularization.[27] Although the number of patients evaluated in studies investigating the correlation between metal allergy and ISR is small, this intriguing evidence suggests that metallic hypersensitivity may account for a high percentage of restenosis observed with BMS. In summary, angioplasty with stenting produces the same mechanisms of injury, including endothelial denudation and dissection of the tunica media, but also activates inflammation by lipid core penetration. These events trigger the cellular and molecular cascades described here, eventually leading to neointimal hyperplasia.

DRUG-ELUTING STENTS: PREVENTING RESTENOSIS

Although BMS has markedly reduced the incidence of restenosis, ISR continues to be a major problem. Mechanical strategies, systemic pharmacotherapy, and intravascular brachytherapy are methods used to reduce the frequency of ISR. Mechanical strategies include: 1) IVUS-guided high-pressure deployment to achieve larger mean luminal diameter, 2) the use of thinner stent struts, 3) prior debulking therapy, and 4) avoiding predilation. These strategies have achieved some reduction in restenosis rates but failed to demonstrate a significant benefit in large randomized, controlled trials.[28–30] Systemic administration of agents that inhibit specific processes in restenosis has also been suggested as a possible option. Antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin-converting enzyme inhibitors, statins, and antioxidants have reduced neointimal formation in various animal models. However, the same efficacy has not been observed in randomized trials.[31–36] The downside to systemic pharmacotherapy is the inability to deliver a high dose of the agent to the lesion without inducing systemic side effects. Unlike the previous 2 modalities, intravascular brachytherapy has shown a reduction in neointimal proliferation and ISR in multiple randomized clinical trials.[37–39] However, the lack of an optimal radiation dose, the practical difficulty in scheduling the procedure between radiation oncologists and the catherization laboratory, the edge effect resulting from geographic miss leading to in-lesion restenosis, and increased rates of subacute thrombosis have delayed the wide acceptance of intracoronary radiation into clinical practice.[40,41]

Drug-Eluting Stents' Focus on the Prevention of In-Stent Restenosis

The ability of the stent to deliver an agent locally to the site of injury reduces proliferation of VSMC without causing systemic toxicity. The drug can be delivered by the stent through a variety of mechanisms. The first approach used dipping or spraying the drug on to the BMS.[42] This approach lacks the gradual release that is generated by other methods and instead delivers a large bolus immediately into the local area. A second approach coats the metal stent with degradable or nondegradable biopolymers, which are loaded with the drug and deliver a sustained release of the agent. A drug-free coated polymer layer can be added to function as a diffusion barrier, further controlling the elution kinetics of the agent.[43]

The compatibility of the coated polymer with the vessel wall determines the degree of inflammation that is generated on contact. The majority of polymers used for stent coating have introduced a substantial amount of inflammation in experimental models. The major concerns that arise from the use of polymers include chronic inflammation specifically after the elution is complete, direct local toxicity to the vascular tissue, polymer incompatibility with circulating humoral factors, and polymer breakdown and erosion.[43] The ideal polymer effectively delivers antirestenotic therapy over an appropriate time course and in the process remains biologically inert, tolerates mechanical stress, and is not thrombogenic.[43]

There were many agents used in the preclinical analysis to determine which drug would be the most efficacious in preventing ISR. The 2 agents that have repeatedly shown the most success in preclinical and clinical trials are sirolimus and paclitaxel.

Sirolimus-Eluting Stents

Sirolimus (Rapamycin) is a natural macrocyclic lactone with potent immunosuppressive and antimitotic action produced by a fungus, *Streptomyces hygroscopicus.* In 1999, the U.S. Food and Drug Administration (FDA) approved sirolimus for antirejection in renal transplants.[44] The agent binds intracellularly to FK binding protein-12 (FKBP-12) forming the immunosuppressive complex that inhibits the mammalian target of Rapamycin (mTOR), a key regulatory kinase that leads to an increase in the levels of $p27^{kip1}$. The rise in $p27^{kip1}$ inhibits the cyclin–cyclin-dependent kinase complex, blocking the G_1-S transition and therefore restricting proliferation of VSMC.[45] When bonded to a stent, the effects are achieved locally without the complications of systemic toxicity. The sirolimus-eluting stent generates essentially undetectable levels in peripheral blood.[46] There are 4 pivotal trials conducted with sirolimus-eluting stents (SES) that have generated impressive results that led to their approval by the FDA in April 2004.[47–57] The studies used the Bx-Velocity stent, which is a balloon-expandable design made of tubular grade 316L stainless steel. The platform was coated with 5 μm of coating that consisted of a blend of 33% sirolimus and 67% of nonerod-

able polymer. The drug–polymer matrix contained 140 μg/cm^2 of sirolimus. A drug-free polymer coat served as a diffusion barrier to control drug release such that 80% was released in the first 30 days postimplantation and no residual drug was detected beyond 90 days.[47–57]

The trials used similar methodology, inclusion and exclusion criteria, and protocols. Patients underwent quantitative angiographic analysis to determine late luminal loss (mean luminal diameter after procedure minus the mean luminal diameter at follow up), percent diameter stenosis, and ISR, defined as diameter stenosis (DS) within the stent of greater than 50%. Major adverse cardiac events (MACE) were defined as death, acute myocardial infarction (MI), total vessel failure (TVF), and target lesion revascularization (TLR). TLR was defined as a repeat PTCA or coronary artery bypass grafting (CABG) involving the stented lesion driven by clinical signs of ischemia in the presence of angiographic restenosis. The first human clinical trial was conducted in Brazil where J. Eduardo Sousa and colleagues demonstrated the safety of SES.[47–49] The first European experience with SES was published shortly after the Sao Paolo group showing similar promising results.[50,51]

RAVEL Trial

The RAVEL trial was one of the first multicenter, medium-scale trials that randomized 238 patients to compare the safety and efficacy of BMS (n = 118) and SES (n = 120). The 2 groups were similar with respect to all clinical variables except for a larger percentage of men in the BMS group. Table 1 summarizes the data of the RAVEL and the other major sirolimus trials. At 6 months after the procedure, 211 of 238 (89%) patients underwent angiographic follow up showing a significant reduction in the degree of late luminal loss ($P < 0.001$), in-stent percent DS ($P < 0.001$), and rate of ISR ($P < 0.001$) in the sirolimus group. There was a significant decrease in the incidence of TLR (0.8% vs. 23.7%, $P = 0.001$) and MACE (5.8% vs. 28.8%, $P < 0.001$) in SES versus BMS.[52] The 3-year follow-up data were recently published demonstrating the continued clinical benefit of SES in 227 (95%) patients. The frequency of TLR was 25.7% in BMS and 6.1% in SES ($P < 0.001$). The incidence of MACE was 33.1% in the BMS and 15.8% in the sirolimus cohort ($P = 0.002$). There was no significant difference between the 2 groups with regard to death or MI at 9 months and 3 years.[53]

SIRIUS Trial

The SIRIUS trial enrolled 1058 patients in a randomized, double-blind multicenter trial to determine the clinical benefit of SES (n = 533) in comparison to BMS (n = 525). Each patient received 75 mg of clopidogrel daily for 3 months to reduce the risk of subacute thrombosis. Angiographic follow up was done 8 months postprocedure in 703 (66%) patients and demonstrated a significant decrease in late luminal loss ($P < 0.001$), in in-stent and in-lesion percent DS ($P < 0.001$) in the SES group in comparison to the BMS group. There was a significant reduction in the rate of ISR and in-lesion restenosis ($P < 0.001$) in SES versus BMS. There was a significant decrease in the incidence of TLR (4.1% vs. 16.6%, $P < 0.001$) and MACE (7.1% vs. 18.9%, $P < 0.001$) in SES versus BMS at 9 months.[54] The 3-year clinical follow-up data in 985 (93%) patients showed persistent benefit of SES. The rate of TLR was 23.2% in BMS and 6.8% in SES ($P < 0.0001$). The frequency of MACE was 27.4% in BMS and 12.6% in the sirolimus group ($P < 0.0001$). There was no significant difference between the 2 groups in terms of death, MI, or stent thrombosis at 9 months and 3 years.[55]

TABLE 1. Summary of the Major Randomized, Controlled Trials Involving Sirolimus-Eluting Stents Compared With the Bare Metal Stent Controls

	RAVEL	SIRIUS	C-SIRIUS	E-SIRIUS
No. patients	238	1058	100	352
Lesion length (mm)	9.58	14.4	13.6	15.0
RVD (mm)	2.62	2.80	2.63	2.55
DM (%)	19	26	24	23
Follow up (months)	12	9	9	9
LLL (mm)				
BMS	0.88	1.00	1.02	1.05
SES	−0.01	0.17	0.12	0.20
P	<0.001	<0.001	<0.001	<0.0001
ISR (%)				
BMS	28.8	35.4	45.5	41.7
SES	0.0	3.2	0.0	3.9
P	<0.001	<0.001	<0.001	<0.0001
TLR				
BMS	25.7*	23.2*	18.0	20.9
SES	6.1	6.8	4.0	8.0
P	<0.001	<0.0001	0.05	<0.0001
MACE (%)				
BMS	28.8*	27.4*	18.0	22.6
SES	5.8	12.6	4.0	4.0
P	0.002	<0.0001	0.05	<0.0002

*Three-yr follow-up data.

BMS indicates bare metal stents; DM, diabetes mellitus; ISR, in-stent restenosis; LLL, late lumen loss; MACE, major adverse cardiac events; RVD, reference vessel diameter; SES, sirolimus-eluting stent; TLR, target lesion revascularization.

E-SIRIUS/C-SIRIUS

The E-SIRIUS and the C-SIRIUS trials were randomized, double-blind, multicenter trials that enrolled 352 and 100 patients, respectively, to confirm the successful results found in the RAVEL and SIRIUS trials. Angiographic analysis at 8 months was done on 308 (88%) patients in the E-SIRIUS and 88 (88%) in the C-SIRIUS, and demonstrated a significant reduction in the amount of late luminal loss ($P < 0.001$), in the in-stent and in-lesion percent DS ($P < 0.001$) in SES compared with BMS. The rate of ISR and in-lesion restenosis was significantly lower in patients who received SES compared with their matched control subjects (Table 1). There was a significant decrease in the frequency of TLR and MACE in SES versus BMS ($P < 0.001$) at 9 months. There was no significant difference in the frequency of death or MI between the 2 groups in either of the 2 trials.[56,57]

In summary, the sirolimus trials repeatedly demonstrated significant efficacy and safety with the use of SES in

the prevention of ISR and the reduction of future requirements for revascularization.

Paclitaxel-Eluting Stents

Paclitaxel is a compound isolated from the bark of the Pacific yew tree in northwestern America (*Taxus brevifolia*). Today, the synthetic form of paclitaxel, Taxol, is used in oncology as treatment of breast and ovarian malignancies.[58] Paclitaxel exerts its pharmacologic effect by inhibiting microtubule depolymerization resulting in the formation of numerous decentralized and unorganized microtubules. This results in inhibition of cellular replication at the G_0/G_1 and G_1/M phase, and stops cytokine-mediated induction of cell proliferation and migration.[58] The dosage of paclitaxel that is exposed to the vessel wall also determines the type of response that is generated. At high doses, paclitaxel has been shown to cause inflammatory cell loss, medial thinning, and increase in stent thrombosis.[59]

Analyzing and comparing the different trials that evaluated the efficacy of paclitaxel-eluting stents (PES) is a challenge as a result of the variation in the stent platforms used, protocols, dose densities, and techniques. The best approach is to evaluate the trials in subsets that used similar protocols and, more importantly, stent platform, coating, and polymer carrier if one was used.[60–67]

TAXUS Trials

The first trial in the TAXUS series, TAXUS I, was the first experience in humans with PES. The TAXUS trials I–V used a similar protocol[60–64] involving either the NIRx or the Express stent platform (TAXUS IV, TAXUS V) that was coated with a Translute coating and contained a polymer carrier on the surface. The copolymer system provides homogenous coverage on stent deployment and assures predictable pharmacokinetics of drug delivery. The Translute coating forms a biphasic release of paclitaxel with an initial burst in the first few days and a second release completed by the 10th day. The dose used was 1 $\mu g/mm^2$. Other specifics about trial methodology and protocol have been described elsewhere.[60–64] The relevant data involving paclitaxel polymer coated stents is shown in Table 2.

TAXUS I was a prospective, double-blind, multicenter trial that randomized 61 patients into either the TAXUS or the BMS group using the same stent platform without medication. Angiography at 6 months showed a significant decrease in the late luminal loss ($P = 0.008$) and percent DS ($P < 0.001$) in PES in comparison to BMS. However, as a result of insufficient power of the study, the incidence of ISR, TLR, and MACE was not significantly different.[60]

The TAXUS II trial was a randomized, double-blind, multicenter trial that randomized patients into 2 separate PES groups. Both the slow-release and the moderate-release paclitaxel formulations had their respective controls that were matched for clinical and angiographic variables. At 6 months follow up, there was a significant decrease in the late luminal loss ($P < 0.0001$) and in-stent percent DS ($P < 0.0001$) in both the slow-release and moderate-release groups when compared with their respective controls. The rate of ISR and in-lesion restenosis was significantly lower in both PES

TABLE 2. Summary of the Major Randomized, Controlled Trials Involving the Polymer-Coated Paclitaxel-Eluted Stents in Comparison to Their Matched Controls

	TAXUS I	TAXUS II-MR	TAXUS II-SR	TAXUS IV	TAXUS V
No. of patients	61	269	267	1314	1156
Lesion length (mm)	11.3	10.5	10.6	13.4	17.3
RVD (mm)	2.97	2.70	2.80	2.75	2.69
DM (%)	18.1	15.5	13.5	32.3	30.8
Follow up (months)	12	12	12	9	9
LLL (mm)					
BMS	0.71	0.77	0.79	0.92	0.90
PES	0.36	0.30	0.31	0.39	0.49
P	0.008	<0.0001	<0.0001	<0.001	<0.001
ISR (%)					
BMS	10.0	20.2	17.9	24.4	31.9
PES	0.0	4.7	2.3	5.5	13.7
P	NS	0.0002	0.0002	<0.001	<0.0001
TLR (%)					
BMS	13.3	14.6	12.0	17.4*	15.7
PES	0.0	3.1	4.6	5.6	8.6
P	NS	0.002	0.04	<0.0001	<0.0003
MACE (%)					
BMS	10.0	21.4	22.0	24.9*	21.2
PES	3.0	9.9	10.9	14.7	15.0
P	NS	0.017	0.02	<0.0001	0.008

*Two-yr follow-up data.

BMS indicates bare metal stents; DM, diabetes mellitus; ISR, in-stent restenosis; LLL, late luminal loss; MACE, major adverse cardiac events; MR, moderate release; PES, paclitaxel-eluting stent; RVD, reference vessel diameter; SR, slow release; TLR, target lesion revascularization.

groups compared with their respective controls (Table 2). The 12-month incidence of MACE was significantly lower in the TAXUS groups versus their matched controls ($P = 0.02$). There was no significant difference in the rate of MI or death between either of the PES formulations with their respective BMS groups.[61]

TAXUS IV was a large randomized, double-blind, multicenter trial that enrolled 1314 patients with similar clinical and angiographic variables to determine the efficacy and safety of PES (n = 662) versus BMS (n = 652). Clopidogrel was administered for 6 months after the procedure. Five hundred fifty-nine (43%) patients underwent follow-up angiography that demonstrated a significant reduction in the amount of late lumen loss ($P < 0.001$), in-stent percent DS ($P < 0.001$), and the rate of ISR ($P < 0.001$) in PES compared with BMS. The incidence of TLR (3% vs. 11.3%) and MACE (8.5% vs. 15%) was significantly lower in PES versus BMS ($P < 0.001$). There was no significant difference in the frequency of death from cardiac causes, MI, or stent thrombosis between the 2 groups.[62] The 2-year follow-up clinical data in 1238 (94%) patients demonstrated continued benefit of PES. The rate of TLR was 17.4% in BMS and 5.6% in PES ($P < 0.0001$). The incidence of MACE was 24.9% in BMS and 14.7% in PES ($P < 0.0001$). There was no significant difference in the incidence of cardiac death, MI, or stent thrombosis between the 2 groups.[63]

TAXUS V was a double-blind, multicenter trial that randomized 1172 patients to determine the efficacy of PES in more complex lesions. In the 990 (75%) patients who underwent angiographic follow up at 9 months, there was a significant decrease in the rate of ISR and in-lesion restenosis in the PES group ($P < 0.001$). Clinically, there was a significant decrease in the frequency of TLR ($P < 0.0003$) and MACE ($P = 0.008$) in PES in comparison to BMS. There was no significant difference in the incidence of MI or cardiac death between the 2 cohorts. However, there was an increase in the incidence of MI (8.3% vs. 3.3%, n = 376) at 30 days in the PES versus BMS in the subgroup that received multiple stents ($P = 0.047$). Although the subset analysis was underpowered, the data prompted further studies involving more complex lesions.[64]

ASPECT Trial

The ASPECT trial was a randomized, multicenter, controlled, double-blind study that evaluated the use of PES to reduce ISR. The results of the trial along with the other trials that did not use a polymer coating system are shown in Table 3. The trial also attempted to show a dose-dependent reduction in restenosis by using 2 groups of PES with a dosage of 3.1 $\mu g/mm^2$ and 1.3 $\mu g/mm^2$ with the same controls. One hundred seventy-seven patients were randomized into 3 groups, 60 into the 3.1-PES, 58 into the 1.3-PES, and 59 had BMS. Unlike the TAXUS trial, the ASPECT trial did not use a polymer carrier, but used a proprietary process to bond paclitaxel onto the abluminal surface of the Supra-G stent. Antiplatelet therapy was not standardized with some patients receiving cilostazol in place of clopidogrel. Angiographic analysis conducted in 172 (97%) patients demonstrated a significant dose-dependent reduction in late lumen loss ($P < 0.001$) and percent DS ($P < 0.001$). The incidence of ISR was 4% in the 3.1-PES group, 12% in the 1.3-PES group, and 27% in the BMS group ($P < 0.001$). The rate of TLR was 3.4% in all 3 groups, and the frequency of MACE at 6 months was 5.2% in the BMS and 1.3-PES groups and 11.9% in the 3.1-PES group. The increase in MACE was attributed to an increase in subacute thrombosis in the 3.1-PES group, specifically in the patients who received cilostazol.[65]

TABLE 3. Summary of the Major Randomized, Controlled Trials Involving the Nonpolymer-Coated Paclitaxel-Eluted Stents in Comparison to Their Matched Controls

	ASPECT	ELUTES	DELIVER
Dose ($\mu g/mm^2$)	3.1	2.7	3.0
No. of patients	177	190	1041
Lesion length (mm)	10.9	10.8	11.4
RVD (mm)	2.92	2.96	2.81
DM (%)	20	15.8	28.8
Follow up (months)	6	12	9
LLL (mm)			
BMS	1.04	0.73	0.98
PES	0.29	0.11	0.81
P	<0.001	0.002	0.0025
ISR (%)			
BMS	27.0	20.6	20.6
PES	4.0	3.2	14.9
P	<0.001	0.056	0.02
TLR (%)			
BMS	3.4	15.8	11.3
PES	3.4	5.4	8.1
P	NS	NS	NS
MACE (%)			NR
BMS	5.2	18.4	
PES	11.9	13.5	
P	NS	NS	

BMS indicates bare metal stents; DM, diabetes mellitus; ISR, in-stent restenosis; LLL, late luminal loss; MACE, major adverse cardiac events; NR, not reported; PES, paclitaxel-eluting stent; RVD, reference vessel diameter; TLR, target lesion revascularization.

ELUTES Trial

The ELUTES trial was a randomized, double-blind, controlled trial that evaluated the efficacy and safety of PES without a polymer coating. The cohort of patients was randomized into 5 groups (BMS 0.2 $\mu g/mm^2$, 0.7 $\mu g/mm^2$, 1.4 $\mu g/mm^2$, 2.7 $\mu g/mm^2$) with similar clinical variables except for a significant difference in age between the 0.2 and the 2.7-PES groups ($P = 0.02$). The V-Flex Plus stent was prepared similarly to the method used in the ASPECT trial. Angiography at 6 months showed a significant reduction in late loss ($P = 0.002$), percent DS ($P = 0.006$), and the rate of ISR ($P = 0.056$) only in the 2.7-PES group compared with BMS. The lower dosage PES had no significant difference in any variables in comparison to the BMS. The rates of TLR and MACE were not significantly different between the 5 groups.[66]

DELIVER Trial

The DELIVER trial was a prospective, randomized, placebo-control trial that randomized 1043 patients with sim-

ilar clinical variables into the paclitaxel-coated (3.0 $\mu g/mm^2$) ACHIEVE stent (n = 522) versus the Rx ML PENTA stainless steel stent (n = 519). Angiography at 8 months in 442 (42%) patients demonstrated a significant decrease in the late lumen loss ($P = 0.002$), in-stent ($P = 0.02$) and in-lesion percent DS ($P = 0.04$) in PES in comparison to BMS. There was no significant difference in the incidence of ISR, in-lesion restenosis, or TLR between the 2 groups.[67]

Sirolimus versus Paclitaxel-Eluting Stent Trials

The TAXi trial was the first prospective, randomized trial that compared the efficacy of SES (CYPHER) versus PES (TAXUS). Two hundred two patients with similar demographics were randomized to either SES (n = 102) or PES (n = 100). Although the data showed no significant difference in MACE between SES and PES at 6 months, the trial was limited in its sample size to determine any clinical superiority between the 2 DES.[68]

REALITY Trial

The REALITY trial was a large prospective, randomized trial that compared the polymer-coated SES against the polymer-coated PES in terms of safety and efficacy. The study randomized 1353 patients with similar angiographic and clinical variables into SES (n = 684) and PES (n = 669) groups with the primary end point of in-lesion restenosis rate at 8 months. The data from the REALITY trial as well as other PES versus SES trials is shown in Table 4. The trial demonstrated a significant decrease in the in-stent, in-lesion percent DS and late luminal loss in patients treated with SES in comparison to PES ($P < 0.001$). However, the incidence of in-lesion, ISR, TLR, MACE, MI, or cardiac death was not significantly different between the 2 groups at 9 months. Interestingly, the rate of vessel thrombosis at 30 days was significantly lower (0.4% vs. 1.8%, $P = 0.02$) in SES versus PES. The decrease in 30-day vessel thrombosis with SES raised concern about the long-term safety of PES versus SES but may also have been a statistical aberrancy.[69]

SIRTAX Trial

SIRTAX was a prospective, randomized trial that compared the efficacy of SES against PES. The study randomized 1012 patients with similar clinical and angiographic variables into SES (n = 503) and PES (n = 509) with the primary end point of MACE at 9 months. Follow-up angiography in 540 (53.4%) patients showed a significant decrease in late lumen loss ($P < 0.001$) in the SES group. The rate of ISR and in-lesion restenosis was significantly lower in the SES group ($P < 0.02$) at 9 months. The incidence of TLR was 4.8% in SES and 8.3% in PES ($P = 0.025$), and the frequency of MACE was 6.2% in the sirolimus and 10.8% in the paclitaxel group ($P = 0.009$). Not unexpectedly, there was no significant difference in the rates of death, cardiac death, MI, or stent thrombosis between the 2 groups.[70]

ISAR-DESIRE Trial

In distinction to the previous trials that assessed DES to prevent restenosis, ISAR-DESIRE was a prospective, randomized, controlled trial that assessed the efficacy of DES in the treatment of ISR in comparison to conventional balloon angioplasty. Three hundred patients with similar clinical variables and documented angiographic ISR were randomized to receive SES (n = 100), PES (n = 100), or balloon angioplasty (n = 100). Angiographic analysis preformed in 275 (92%) patients showed a significant decrease in rates of restenosis in both DES cohorts in comparison to balloon angioplasty at 9 months. A secondary analysis comparing the 2 DES showed a significant decrease in late lumen loss ($P = 0.004$) and in-stent percent DS ($P = 0.004$) in SES versus PES. There were lower rates of in-stent, in-lesion restenosis and MACE that did not reach significance in the SES group. There was no significant difference in the incidence of death or MI across all 3 groups.[71]

ISAR-DIABETES Trial

ISAR-DIABETES was a randomized trial that evaluated whether PES showed similar efficacy as SES in the management of patients with diabetes. Two hundred fifty patients were randomized 1:1 to receive either SES or PES. The trial showed a significant decrease in late lumen loss ($P < 0.001$), percent DS ($P = 0.004$) in the SES group. There was a significant decrease in the incidence of ISR and in-lesion restenosis ($P = 0.02$) in SES versus PES. The frequency of TLR was 6.4% in the SES and 12% in the PES group, which is almost double the incidence, but failed to reach statistical significance at 9 months as a result of the

TABLE 4. Summary of the Randomized Clinical Trials Comparing the Efficacy of sirolimus With Paclitaxel-Eluting Stents

	REALITY	SIRTAX	ISAR-DESIRE	ISAR-DIABETES
No. patients	1353	1012	200	250
Lesion length (mm)	17.1	12.9	11.95	13.1
RVD (mm)	2.40	2.83	2.60	2.73
DM (%)	27.9	19.9	21.5	100
Follow up (months)	8	9	12	9
LLL (mm)				
SES	0.09	0.12	0.10	0.19
PES	0.31	0.25	0.26	0.46
P	<0.001	<0.001	0.009	<0.001
ISR (%)				
SES	7.0	3.2	11.0	4.9
PES	8.3	7.5	18.5	13.6
P	NS	0.013	NS	0.02
TLR (%)				
SES	5.0	4.8	8.0*	6.4
PES	5.4	8.3	19.0	12.0
P	NS	0.025	NS	NS
MACE (%)				NR
SES	9.2	6.2	11.0	
PES	10.6	10.8	22.0	
P	NS	0.009	NS	

*Target vessel revascularization.

DM indicates diabetes mellitus; ISR, in-stent restenosis; LLL, late lumen loss; MACE, major adverse cardiac events; NR, not reported; PES, paclitaxel-eluting stent; RVD, reference vessel diameter; SES, sirolimus-eluting stents; TLR, target lesion revascularization.

number of cases. There was no significant difference in the incidence of death or MI in the 2 treatment arms.[72]

Sirolimus-Eluting Stents versus Coronary Artery Bypass Graft Trial

ARTS II Trial

ARTS II was a multicenter, nonrandomized, open-label trial that evaluated the effectiveness of SES versus CABG in the prevention of future revascularization and major adverse cardiac and cerebrovascular events (MACCE) in patients with multivessel disease. A group of 607 patients that received SES was compared with the CABG cohort (n = 602) from the ARTS I trial. This was a historical control group and not a contemporary randomized trial. Nevertheless, the surgical results of the ARTS I Trial were excellent compared with other CABG trials. At 1-year follow up, the rate of percutaneous revascularization was 5.4% in the SES and 3.0% in the CABG group (P = not significant [NS]), and surgical revascularization was 2.0% in the SES and 0.7% in the CABG group (P = NS). The incidence of MACCE was 10.2% in the SES and 11.6% in the CABG cohort (P = NS). The rate of death, stroke, and MI was significantly lower with SES in comparison to CABG ($P < 0.001$). Although the trial was a retrospective analysis, it suggests that SES may provide a safer alternative to surgery with equivalent efficacy in patients with multivessel disease. Prospective, randomized, controlled trials will be required to directly compare the effectiveness of angioplasty with drug-eluting stent implantation at decreasing revascularization while simultaneously reducing the cardiovascular morbidity associated with surgery.[73] These preliminary results are encouraging and suggest that angioplasty may have finally reached the goal of providing a true alternative to bypass surgery for the majority of patients with CAD.

DISCUSSION AND CONCLUSION

Restenosis has been a limiting factor to the clinical success of percutaneous coronary intervention. The introduction of stents significantly reduced rates of restenosis by eliminating elastic recoil and negative remodeling. However, the augmented inflammatory response that leads to an increase in neointimal hyperplasia associated with stenting initiated a new challenge in interventional cardiology: ISR. Understanding the pathophysiology of restenosis, and specifically ISR, on a cellular and molecular level allows for the development of targeted therapy. DES deliver antiproliferative agents at effective doses to an area that experiences intense inflammation, thus reducing neointimal formation without reaching toxic levels in the blood.[46] Some of the earlier concerns surrounding DES was its increased propensity to cause coronary aneurysms based on experimental animal data.[74] There were warnings that the drug or the polymer could damage the vessel, leading to progressive luminal dilation, aneurysm formation, and predispose the vessel to thrombosis or rupture.[74] However, none of the major clinical trials that compared either SES or PES with BMS showed a significant difference in aneurysm formation between the 2 groups.[52,54,56,57,60–63] The wide use of DES has brought forth another concern of subacute stent thrombosis that may result in a catastrophic cardiac event. The use of aspirin and clopidogrel is crucial in preventing subacute stent thrombosis.[75] The major clinical trials involving sirolimus and paclitaxel demonstrated a total thrombosis rate of 0.4% and 0.6%, respectively.[54,62] However, the majority of the patients in these trials presented with relatively simple lesions. With the increased use of DES in patients with acute MI, bifurcation lesions, treatment of ISR, the rate of subacute stent thrombosis may increase. A recent prospective, observational study that enrolled a total of 2229 consecutive patients who underwent stenting with either SES or PES attempted to provide more accurate data by evaluating patients with complicated lesions.[76] At 9 months, 29 (1.3%) patients had stent thrombosis and 14 (0.6%) patients developed subacute thrombosis with a case-fatality rate of 45%. The most common predictor of stent thrombosis was premature discontinuation of antiplatelet therapy. Early discontinuation of antiplatelet therapy is associated with a 30-fold increase in incidence of stent thrombosis.[77] Other independent predictors included renal failure, bifurcation lesions, diabetes, low ejection fraction, and stent length.[76] Although the rate of stent thrombosis in this observational study was significantly higher, the absolute number of cases is still low. Given the consequences that result from stent thrombosis, it is critical that patients and their physicians are educated regarding continuing their antiplatelet therapy with aspirin and clopidogrel. The duration of therapy may need to be increased in patients with more complicated lesions, although that conclusion will have to be drawn from further randomized, controlled trials.

In reviewing the data from major randomized trials involving SES and PES, one can appreciate the potential of DES. Approximately 3160 patients were evaluated in the Bx-Velocity SES and 4201 were evaluated in studies involving the TAXUS stent. The angiographic data is impressive. SES produces a remarkable reduction in late luminal loss, diameter stenosis, and neointimal hyperplasia demonstrating the effectiveness of sirolimus in inhibiting rapidly proliferating VSMC. The reduction in ISR to less than 5% of the lesions underlines the success sirolimus stents have at keeping the vessel patent. Clinically, SES was successful in significantly reducing MACE by decreasing the requirement for revascularization. In none of the sirolimus trials was there a mortality benefit or a significant reduction in the incidence of MI. The efficacy and safety of sirolimus up to 4 years of follow up indicates that the coated polymer stent loaded with 1 $\mu g/mm^2$ of sirolimus serves as an effective agent in the prevention of ISR. The coated polymer controls the release kinetics to provide an initial burst of sirolimus at the time of a high rate of proliferation and a basal elution for inhibition of neointimal formation within the critical window of the first month.

The paclitaxel trials can be divided into 2 groups. The first is the TAXUS trials,[60–64] which used a coated polymer and repeatedly demonstrated significant reduction in late loss, diameter stenosis, and neointimal hyperplasia. The reduction in the incidence of ISR is not as dramatic as observed in the

sirolimus trials but is significant. The rate of MACE at 1 year was again reduced significantly by decreasing the need for revascularization; however, there was no reduction in the incidence of MI or cardiac mortality. The second group of trials (ASPECT, ELUTES, DELIVER)[65–67] did not use a polymer-coated stent and failed to demonstrate a clinical benefit in terms of MACE or prevention of future revascularization. The trials also showed that an increased paclitaxel dose was required to produce a significant angiographic benefit that was comparable to the TAXUS or sirolimus groups. The controlled release of the drug with the coated polymer generates a greater angiographic benefit and more favorable clinical outcomes. The lack of polymer requires the use of higher doses of antiproliferative agents that perhaps induce injury to the vessel wall, reducing the benefit of PES, and thus does not show improvement in clinical outcomes.

Although DES have demonstrated safety and efficacy, there are numerous unresolved issues. The number of study patients who received these stents is still relatively small. The lesions treated in these trials are relatively simple in the sense that the lesion length is short, the reference vessel diameter is large, and the percentage of patients with diabetes is small, which are all factors that will lower the rate of restenosis. In addition, the majority of the trials enrolled patients without previous interventions. The TAXUS III trial treated a cohort of 28 patients with ISR without controls. The repeat restenosis rate was 16%. The benefit in terms of late loss and MACE was reduced compared with the results reported in previous trials involving PES.[78] The issue of edge restenosis appears to be resolved. Previously, there was a concern that the uneven distribution of the agent would deliver less drug to the edges, thus reducing ISR but increasing in-lesion restenosis.[79] The studies that reported the in-lesion percent DS and incidence of in-lesion restenosis demonstrated that there was no significant difference in edge restenosis between DES and the BMS group.[80] Stent malapposition is another potential problem detected by IVUS that is increased in the SES group in comparison to the controls in the SIRIUS and RAVEL trials at 6 months.[52,54] Such findings were not observed in the TAXUS-II trial.[61] However, these observations have not been associated with any adverse events to date.

In addition, there is limited data involving DES in complex lesion subsets that include acute MI, bifurcation lesions, left main disease, and saphenous vein grafts. The majority of the clinical trials excluded patients that presented such therapeutic challenges. Recently, some of these subsets have been investigated in clinical trials. The STRATEGY trial was the first randomized, single-center trial that randomized 175 patients to evaluate the effectiveness of SES versus BMS in acute MI. The trial demonstrated significant reduction in late loss, ISR (7.5% vs. 28%, $P = 0.01$), in-lesion restenosis, and TLR (6% vs. 20%, $P = 0.006$) in SES versus BMS at 8 months. There was no significant difference in the rate of death, reinfarction, or stent thrombosis at 30 days and 8 months.[80] The data is comparable to the RESEARCH registry that showed a significant decrease in MACE (9.4% vs. 17%, $P = 0.02$) and TVR (1.1% vs. 8.2%, $P < 0.01$) in SES versus BMS at 10 months follow up. Again, there was no significant difference in the incidence of stent thrombosis, death, or reinfarction at 30 and 300 days.[81] The preliminary clinical data suggests that SES is as safe as BMS when used during acute MI and appear to produce less restenosis in this setting as well.

Another unresolved issue is the role of DES in the treatment of bifurcation lesions. Historically, stenting of the side branch has yielded a high restenosis rate (30%).[82] Prospective, as well as retrospective, data involving either SES or PES was unable to show any angiographic or clinical benefit with stenting of the side branch compared with provisional stenting.[83–86] Stent malapposition, breakage of polymer secondary to the overlap of multiple strut layers, and uneven distribution of struts may account for the lack of benefit with side branch stenting.[83] The "crush" technique reduces stent malapposition and may show improvement in clinical and angiographic parameters.[85] One of the main concerns regarding stenting both the main branch and the side branch is the increased risk of both postprocedural and subacute stent thrombosis.[83–86] The failure to use periprocedural glycoprotein IIb/IIIA inhibitors and premature discontinuation of antiplatelet therapy was largely responsible for an increased incidence of stent thrombosis.[83–86] Although the DES experience with bifurcation lesions is limited and leaves many unresolved issues, compared with historical BMS controls, DES reduce the incidence of restenosis and TLR in bifurcation lesions.[86] Only large randomized trials involving bifurcation lesions will establish the appropriate procedural technique, the benefit of side branch stenting, and the ideal duration of antiplatelet therapy.

The use of DES as treatment of unprotected left main disease is another unresolved area of DES. Traditionally, unprotected lesions in the left main are an indication for surgical revascularization.[87] Recently, retrospective and small prospective studies demonstrated the safety of DES in the treatment of unprotected left main disease.[87–89] In comparison to historical BMS controls, DES showed a reduction in the rates of MI, MACE, and TVR at 6 months and 1 year, calling for a randomized trial comparing DES versus surgery in unprotected left main lesions.[87,89] Lastly, the use of DES in the treatment of saphenous vein graft lesions is beginning to be explored. Past studies estimate that at least 50% of saphenous vein graft lesions will develop stenosis or occlusion within 10 years of implantation.[90] Given the higher morbidity and mortality associated with repeat surgical revascularization, percutaneous coronary intervention is a preferred option.[90] Although BMS improved outcomes in saphenous vein graft lesions compared with balloon angioplasty, the rates of ISR remain elevated (20–37%).[90] A retrospective analysis that compared DES versus historical BMS controls showed a reduction in restenosis (10% vs. 26.7%, $P = 0.03$), TLR, and MACE at 6 months, demonstrating the safety of DES in these lesions.[90] Given that 4% to 7% of stented saphenous vein graft lesions developed late occlusion, the safety of DES will be evaluated only with long-term follow up and more clinical trial data.[90]

Other questions such as whether DES only delay eventual restenosis can only be answered with longer follow up.

The 3-year follow-up data from the RAVEL trial suggests that the reduction in TLR and MACE obtained from SES is attenuated at 3 years compared with 1 year. However, the SIRIUS trial showed persistent benefit at 3 years follow up in reducing the incidence of TLR and MACE in the SES group. This discrepancy will be resolved with further follow up from both the sirolimus and paclitaxel groups. In addition, the long-term compatibility of the coated polymer with the vessel remains to be seen. Early polymers were proinflammatory within the vasculature, exaggerating neointimal hyperplasia.[43] It is conceivable that the polymer may produce chronic hypersensitivity vasculitis that could lead to neointimal proliferation and vessel occlusion. Only long-term follow up will be able to determine if such problems will arise.

The lack of mortality benefit may be a concern for practitioners in the community. However, the absence of a mortality benefit in drug-eluting stent clinical trials is consistent with the fact that angioplasty has repeatedly failed to show improvement in mortality in patients with stable CAD. This is attributed to the high crossover of medically treated patients to PTCA once they become unstable. Angioplasty, as an extension of medical therapy, reduces angina, limitation of activities of daily living, decreases hospitalization, and provides a less invasive alternative to surgical revascularization. These benefits need to be balanced with the excess cost to the healthcare system that comes with the use of these stents.[91]

Another issue that will continue to evolve with the introduction of new drug-eluting stent platforms and pharmaceuticals is to decide which coated stent is clinically superior and should be used as the mainstream therapy for CAD. A recent meta-analysis attempted to resolve the conflict of which stent provides the most benefit.[92] Although the sirolimus-eluting stent was superior in reducing the rates of restenosis and TVR, the incidence of death, MI, and stent thrombosis was similar.[92] Further follow up and more studies will address which drug-eluting stent may be clinically superior.

The cost of DES has also been a major limiting factor to the wide use of this intervention. Based on the cost analysis conducted by Cohen et al, it is estimated that there is approximately a difference of $2000 between the DES and the BMS, thus an extra $2.4 billion would be added in procedural costs yearly if any DES are used. However, the reduction in the need for further PCI or CABG reduces that amount to $1.5 billion each year.[93,94] Well-informed patients understand the clinical and angiographic benefits of drug-eluting stents that have been demonstrated in large-scale randomized clinical trials. Patients request these stents that provide a preventive strategy to ISR. Perhaps as newer antiproliferative agents and improved stent platforms are approved by the FDA, the cost of DES will be appreciably reduced.

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